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SPINA BIFIDA AND CRANIUM BIFIDUM*

II. Surgical Treatment

FRANC D. INGRAHAM, M.D.,† AND HANNIBAL HAMLIN, M.D.‡

BOSTON

THE treatment of myelomeningocele and encephalocele constitutes one of the major problems of pediatric neurosurgery. The lesion may occur at any point of the dorsal axis, usually but not invariably associated with bifid vertebral anomalies or defects in the skull. These protrusions exhibit great diversity in appearance and histologic components. The distribution, frequency of various types and so forth have been tabulated in a previous communication[1] and the clinical features have been repeatedly described.

Pathologically, myelomeningocele is regarded as representing the result of incomplete and abnormal dorsal fusion that takes place relatively early in embryologic life. The defect or defects thereby produced involve structures inherent to and surrounding the central canal and its contents in variable degree at one or several segments, which may be conjoined or separated by normal intervening anatomical units.

The selection of patients who are likely to be amenable to long-range rehabilitation and the choice of the proper time for operation are of paramount consideration before the question of surgical procedure arises. In some cases the membrane may be so thin and fragile that operation must be carried out immediately to avoid rupture and subsequent meningitis. Occasionally we have removed such protrusions the first day of life, in spite of the fact that it was impossible to give an adequate prognosis at such an early age. Usually, however, there is no need for haste and careful evaluation of the infant, including roentgenologic examination, should be made. The size of the lesion and the nature of its protective coverings are noted. Many of the more formidable ones have a central sac or loculation that is covered externally by a relatively large area of delicate membrane, and one is obliged to await peripheral epithelialization to obtain sufficient tissue for closure, even though the skin eventually available may be cicatrized, uneven and of poor tensile strength.

There may be additional scoliosis, vertebral fusion, absence of ribs or other skeletal abnormalities. Predominating in lumbosacral lesions, talipes equinovarus or valgus is often present and is likely to be accompanied by faulty innervation of the sphincters and lower limbs. Inept control of the latter may not be apparent for weeks or months. Clubfoot deformity and paralysis presage a long course of orthopedic treatment, which can be instituted immediately but often cannot be satisfactorily continued until the tumefaction of the lower back is reduced and given adequate skin protection. These factors combine to produce confusion and indicate that temporization with home care and out-patient visits forms the proper basis of treatment until the infant can be fairly appraised with respect to future promise. There are patients with open marsupialization of the lesion who will not survive long. Other handicaps, particularly poor mental endowment, render surgical success highly improbable. On the other hand, certain patients in whom the outlook seems to be almost hopeless during the early months of life will in time progress to a point where surgery is both feasible and advisable. For example, an infant is examined at a few weeks of age and is found to have a myelomeningocele surrounded by barely enough skin for closure; there are also clubfoot deformity, marked neurologic disorders and hydrocephalus. At the age of two the hydrocephalus has stabilized and the child shows adequate sphincter control and a chronological mental status. Epithelialization of the lesion has great-

*From the Department of Surgery of the Children's Hospital and of the Harvard Medical School.

†Neurosurgeon, Children's Hospital; associate in neurosurgery, Peter Bent Brigham Hospital; associate in surgery, Harvard Medical School.

‡Formerly, fellow in neurosurgery, Children's Hospital, and assistant in surgery, Harvard Medical School.

ly reduced the operative risk; after successful repair the residual physical disability can receive full benefit of orthopedic surgery. One must be very slow to give a definite prognosis in such cases, even in the severe grades of the deformity.

Among the congenital anomalies associated with myelomeningocele, hydrocephalus offers the greatest difficulty from the standpoint of selection of cases for surgery and their prognosis. The abnormality may be recognizable at birth with palpable diastasis of fontanelles and cranial sutures and craniolacunia (*Lükenschädel*) present roentgenographically. Conservative home care is obviously to be recommended as the initial phase of treatment in such cases. Sometimes, however, the disturbance is insidious, enlargement of the head becoming apparent shortly after the myelomeningocele has been well repaired. Repetition of this sequence of events is probably responsible for the myth that removal of a meningocele and its spinal fluid reservoir is liable to cause an ensuing hydrocephalus. Delay in surgical intervention, therefore, is the wisest general course to pursue even in some of the simpler forms of the syndrome. The small meningoceles, especially the cervicodorsal protrusions, in infants who are neurologically normal and show no roentgen defect other than a localized spina bifida can be operated on during the first days or weeks of life with a good outlook. The complicated cases, however, in which the myelomeningocele usually is lumbosacral, compel a decision to wait until accurate appraisal of the problem can be formulated during the early period of rapid growth and development. Thus, the best surgical procedure for the given situation and its aftermath, which may be the most perplexing part of the treatment, is carried out with confidence.

The most important feature of the actual operation is the adaptation of whatever technic is used to the case in hand. The elaborate approach necessary to deal safely with nasopharyngeal protrusions will be described in a later communication. The specialized treatment of orbital protrusions has been described by Dandy.[2] Anterior protrusions into the thoracic and abdominal cavities should not be difficult to deal with if a meticulous closure of dura is made and is reinforced by bringing stronger adjacent tissues together over the closure. The disastrous result of failing to make a secure dural closure is illustrated by the following case history.

Case 1 (C. H. 168203). A 5-month-old male infant was transferred to the Surgical Service on February 14, 1933, for treatment of a retrorectal tumor. The patient had been admitted with a history of dysuria and oliguria of 16 days' duration. During this time there had been progressive distention of the abdomen and increasing constipation. Catheterization had been necessary at frequent intervals.

Physical examination showed a well-developed and well-nourished infant in no apparent distress. A soft, smooth, rounded mass the size of a small orange was palpable by rectal examination about 6 cm. above the anal sphincter. X-ray examination showed marked distortion of the large-bowel shadow by the pelvic mass (Fig. 1). Two days later, abdominal exploration was carried out and the cystic mass found to fill the entire pelvis. It was separated from the surrounding structures down to the sacrum, where it was found to be densely adherent. At this point the cyst was aspirated and clear, faintly yellow fluid was removed. It was thought that total removal was impossible, and a portion of the wall was excised, permitting the fluid to drain into the peritoneal cavity. Following operation there were severe vomiting and diarrhea, which gradually subsided. As the general condition improved rectal examination showed that the cyst had reformed. Nineteen days after the first exploration a secondary operation was done and the sac was sutured to the peritoneum. The patient's condition was extremely poor at the end of this procedure and he died 28 hours later.

Figure 1. *Barium Enema Showing Marked Displacement of the Large Bowel by a Pelvic Anterior Meningocele.*

Permission for autopsy was not obtained, but sections of the cyst wall showed it to be undoubtedly the wall of a myelomeningocele containing typical dura and a small, irregular mass of glial tissue.

In retrospect it seems relatively certain that the vital step in the operative procedure in this case — that is, firm closure of the sac — was entirely omitted. Total removal of the sac was apparently impossible but was also unnecessary, and firm closure of the remaining portion, with the formation of a small secondary meningocele, would probably have given a satisfactory result.

FIGURE 2. *Simple Cranial Meningocele with Only a Small Stalk Extending within the Cranial Cavity.*

Protrusions through the cranial vault are relatively simple to deal with. The bony defect is not unusually large, and firm closure of the dura and galea, with the incision adapted to the size and shape of the defect, are all that is necessary (Fig. 2). Low occipital encephaloceles are likely to present a much more complicated problem. These masses are sometimes extremely large, and the decision whether or not operation should be done may be difficult. If marked abnormality of the brain or poor function below the lesion is demonstrable, operation should not be considered. Occasionally one sees an extremely large occipital meningocele or encephalocele that gives the impression of a hopeless outlook when the brain is actually normal (Fig. 3). It is advisable to postpone any estimate of the prognosis until a complete study has been carried out.

The two essential features of any operation on the commoner protrusions — that is, cervical, dorsal, lumbar and lumbosacral (Figs. 4, 5, 6 and 7) — are tight closure of the sac and firm closure of the skin and subcutaneous tissue. Reinforcement of the closure with fascial leaves is desirable if this can be done without prolonging the operation unduly. Reconstruction of the bony canal should never be attempted at this time, but if the defect is such that the bony spine is seriously weakened, a secondary procedure with a bone graft may be done. If the patient is given proper orthopedic care, this should seldom be necessary. In the typical case an elliptical incision (Figs. 8 and 9) is made around the base of the mass, preferably preserving enough healthy skin to be brought together without tension. If this is impossible and operation cannot be postponed until there is enough skin, counterincisions may be made or a Z flap of skin brought over the defect. In the case of lumbar and lumbosacral lesions, the incision should always be made transversely so as to keep the wound as far as possible from the intergluteal fold.

Dissection is carried down to the neck of the sac, carefully avoiding any nerve elements that may be running out from the sac. The sac is then opened through an area, preferably midline, that can be shown to be free from nerve tissue. The interior of the cavity is inspected, nerve tissue

ending in the wall is sacrificed, and nerves that may possibly be functioning are carefully preserved. The major portion of the sac is then cut away, leaving sufficient tissue to overlap the edges enough to make a secure closure. If there is a large amount of tissue that may have potential function, it may be necessary to create a small secondary meningocele to preserve it. In our experience, plication of the sac, as advocated by Penfield,[3] has had no bearing on the development of hydrocephalus postoperatively. In fact, the meningoceles with sufficient skin to make plication of the sac possible are those milder grades of maldevelopment in which one would not expect hydrocephalus to be present.

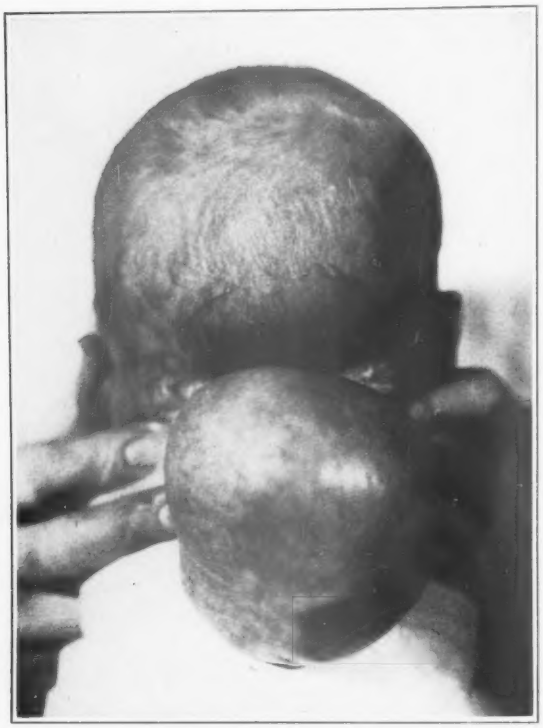

FIGURE 3. *Large Occipitocervical Encephalomeningocele Removed at the Age of Two Weeks.*

The first postoperative week is an extremely critical period because of the danger of spinal-fluid leakage, infection at the closure site and possibly meningitis. The hazard increases with the size and complexity of the lesion. If there is any doubt about the possibility of making a firm closure, prophylactic administration of a sulfonamide, preferably sulfadiazine, is recommended starting forty-eight hours prior to anesthesia and maintaining an effective blood level for at least one week. Ideal aftercare consists of proper initial and subsequent dressing of the wound and the use of specialized methods for regulating cerebrospinal-fluid pressure. Diligent nursing is essential. Complications, if they arise, should be recognized and treated quickly. The particular problems in the postoperative care of the lumbar and lumbosacral types of protrusion are discussed in some detail below.

Before the wound itself is dressed following operation, an apron of sheet rubber or strong oiled silk is glued across the buttocks below the surgical field to protect this area from contamination by excreta.

A routine dressing of sterile sponges over silver foil covering the skin is satisfactory for the small, well-approximated incision, which is the result in many lesions. Anxiety about delayed healing and spinal-fluid leakage is more likely to be felt in the lumbosacral type. When good approximation is achieved following the evacuation and obliteration by suture of a large subcutaneous meningocele, the skin flaps, despite exact alignment, are sometimes loose. In this situation, dead space between the fascial planes can be minimized during the important stage of primary union by taping a small sandbag on the dressing and leaving it there for twenty-four to forty-eight hours. The pad of sponges should be fastened to the skin with adhesive strips running at right angles to one another, leaving interstices of gauze exposed for circulation of air.

In addition to meticulous dressing, conscientious nursing in the supervision of a few specialized technics, adapted to the aftercare of these patients, contributes toward shortening their immobilization, which is usually prolonged under the best conditions. Figure 10 shows the basic setup used postoperatively at the Children's Hospital for cases of myelomeningocele. A Bradford frame is supported by blocks front and back on the mattress of an ordinary crib bed with side drops. The usual rubber sheet crosses the midportion of the mattress, upon which a bedpan rests beneath an overlying aperture in the canvas. A half-cylinder frame keeps the bedclothes away from the surgical area. A clean diaper is kept under the protective apron, which is sealed off above the buttocks. Diapers are applied in the usual fashion when there is no risk of contaminating the dressing or when healing is well advanced. Fitted on the supportive swathes of the Bradford frame are mattress covers over which are stretched and taped layers of Pliofilm or cellophane, which afford excellent protection to infant skin. The patient lies prone as illustrated, and is so maintained by cloth binders around the trunk and upper thighs and a combination of wrist, shoulder and ankle restraints, well padded with sheet wadding. The restraints are varied accord-

FIGURE 4. *Same Patient as in Figure 3, Seven and a Half Years after Operation.*

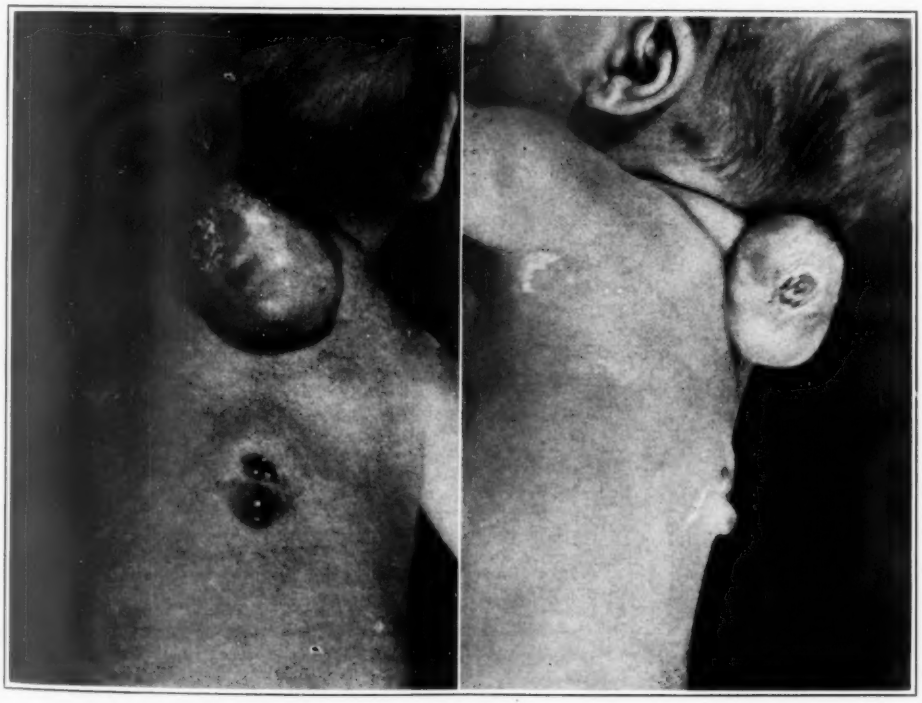

FIGURE 5. *Combined Cervicodorsal and Lower Dorsal Myelomeningoceles, without Impairment of Function.*

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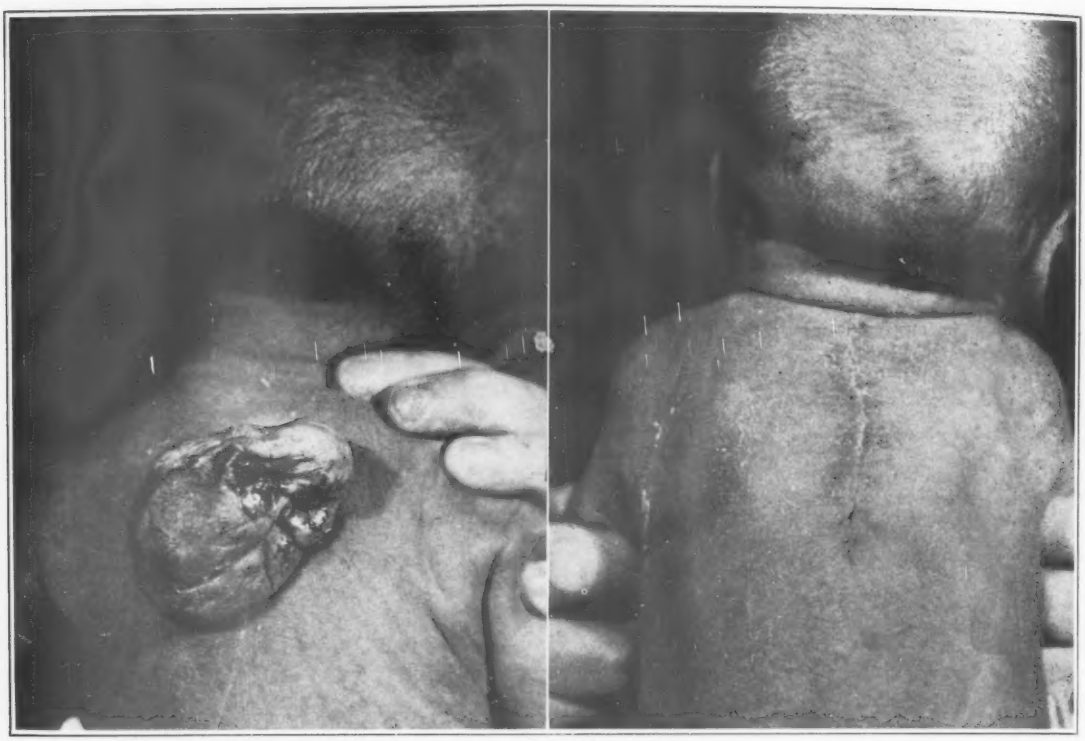

FIGURE 6. *Preoperative and Postoperative Photographs of a Sixteen-Day-Old Infant with a Large Dorsal Myelomeningocele.*

FIGURE 7. *Large Myelomeningocele Involving the Lower Dorsal and All Lumbar and Sacral Segments.*

The patient had an arrested hydrocephalus, and paralysis of the lower extremities and sphincters. The case was not suitable for operation.

ing to the horizontal plane of the frame but with constant regard for maximum comfort. Feeding, bathing and other nursing details are easily accomplished, since the whole frame can be picked up and moved whenever necessary without disturbing the patient. As convalescence progresses the child is allowed gradual freedom of posture by altering the restraints until he is completely mobilized.

If there is undue tension or other reason for examining the wound at frequent intervals, a transparent dressing can be easily prepared (Fig. 11). By this means the operative field can be inspected without removing the dressing and given immediate care should the need arise. Overtight stitches are removed before necrosis starts; any point of the suture line that appears weak may be sealed by a cutaneous silver clip and an incipi-

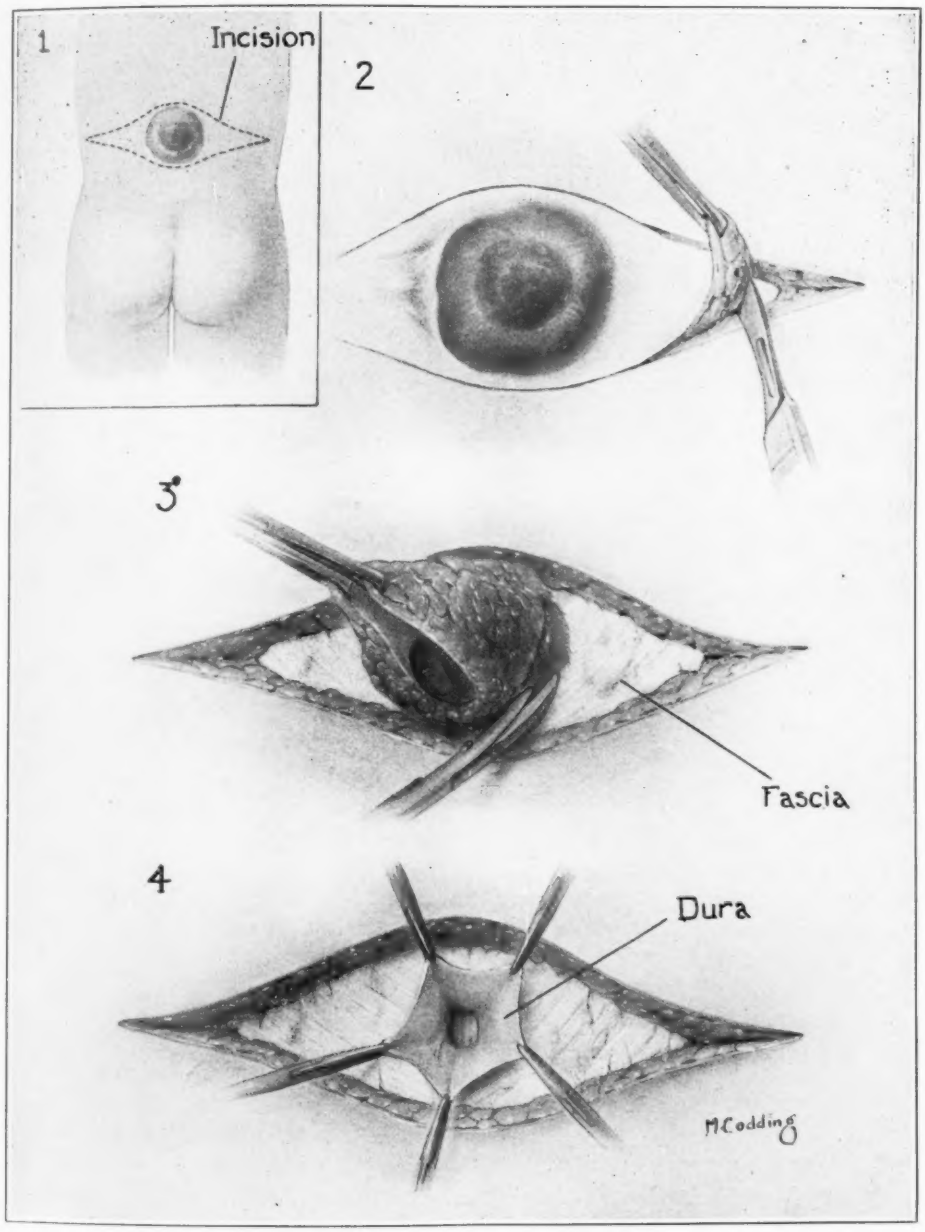

FIGURE 8. *Type of Incision and Dissection Used for Most Lumbar and Lumbosacral Protrusions.*

ent leak perhaps prevented. If superficial infection develops, it can be checked at the onset. A wall of gauze at least 5 cm. deep is built around the wound by layering sponges folded or trimmed to appropriate size. These are secured to the skin and to one another by means of sterile glue, such as Mastisol. A piece of transparent plastic material is then cut to overlap generously the opening in the dressing. Finally the whole is bound down with adhesive bandage and tape. If spinal-fluid leakage is detected during the critical stage of healing, the development of a fistula is preventable by prompt measures such as applications of warm physiologic saline solution and the reduction of intracranial pressure by lumbar puncture or ventricular drainage. If all goes well, the window is left for eight to ten days, at the end of which time a conventional dressing can be substituted.

Occasionally, in spite of all precautions, temporarily increased cerebrospinal-fluid pressure becomes a serious menace. In these cases gravity can be utilized to a certain degree by keeping the head end of the Bradford frame several centimeters lower than the foot with proper-sized blocks. In lumbosacral wounds the head-down position requires that extra vigilance be maintained over excretory cleanliness.

Where the pressure is not controllable by periodic tapping, we have used a simple system of

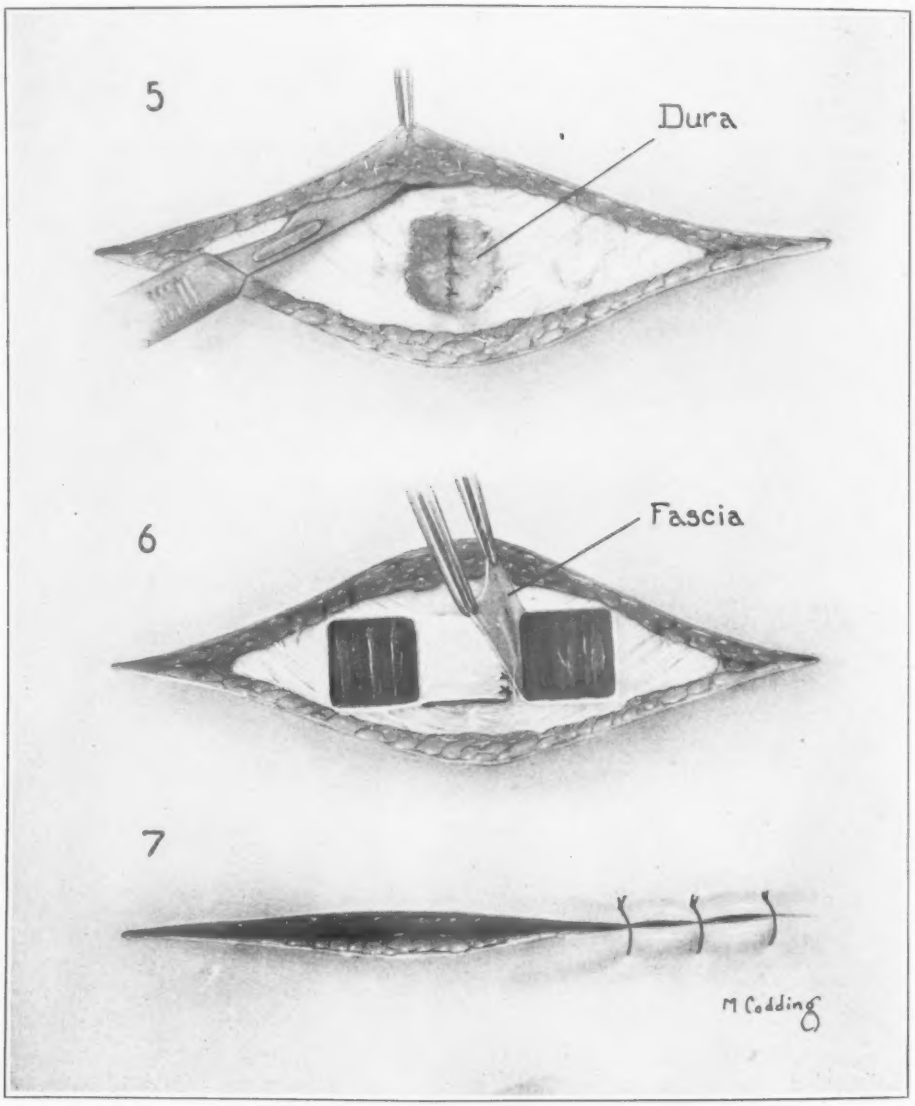

FIGURE 9. *Closure Re-enforced by Fascial Flaps. This step must frequently be omitted.*

constant lumbar drainage that has proved effective. A small-gauge (No. 20) needle is thrust through a sterile cork measuring approximately 3 by 4 cm. and is inserted in the caudal sac at a convenient interspace relative to the dressing. When a free flow of spinal fluid is obtained, the needle is connected by an adapter to an autoclaved gravity apparatus, as shown in Figure 12. The apparatus consists of narrow rubber tubing, broken at one point by a medicine dropper for inspection of patency and connected to a 25-cc. burette. The needle is held perpendicular by taping the cork to the skin. The burette is suspended on the side gate of the crib so that hydrostatics can be regulated to produce the desired rate of flow by raising or lowering the reservoir as indicated by its fluid meniscus. Daily output is measured, and varies according to the time required for stabilization of cerebrospinal-fluid dynamics. An apparatus similar in principle and design was originally described by Ingraham and Campbell[4] for constant ventricular drainage. It can be kept in continuous operation, however, longer by the spinal route than by the ventricular without the risk of meningeal contamination that goes with the latter. This assumes that the dynamics will ultimately stabilize at a physiologic level, which is usually the case if there has not been progressive hydrocephalus preoperatively. If there has been increasing pressure, operation should not have been carried out.

FIGURE 10. *Postoperative Dressing and Immobilization of Patient.*

FIGURE 11. *Postoperative Wound Twenty-four Hours after Application of Transparent Dressing.*

The following summary of the first case of postoperative myelomeningocele in which this technic was applied demonstrates how constant spinal drainage solved a difficult problem of leakage and fistula.

FIGURE 12. *Control of Cerebrospinal Pressure by Continuous Spinal Drainage.*

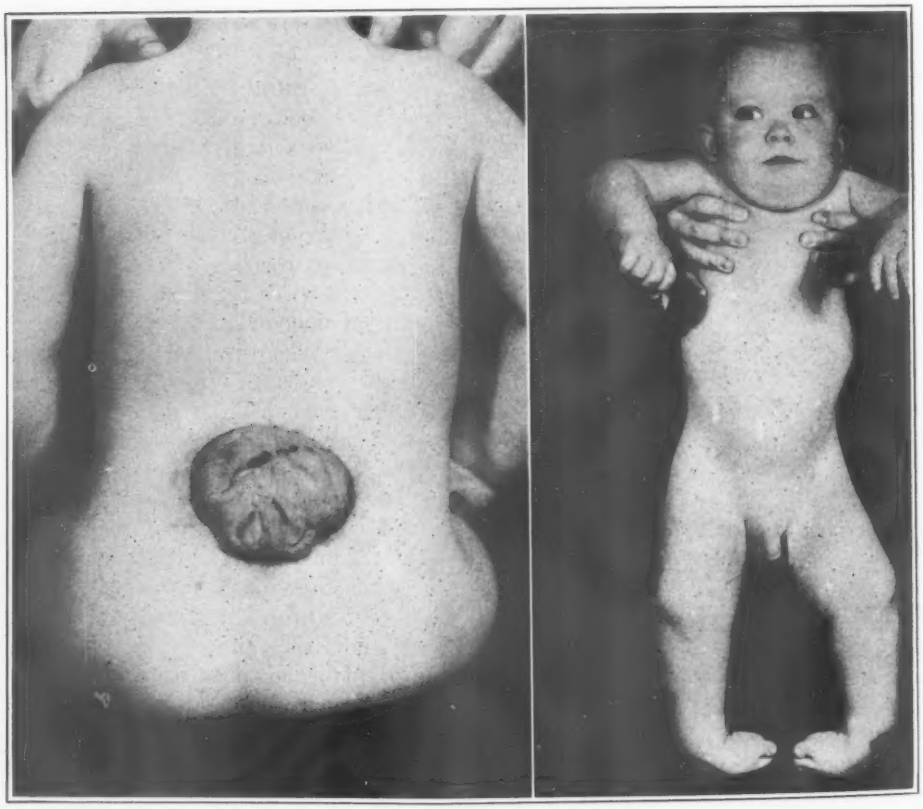

FIGURE 13. *Lumbosacral Myelomeningocele with Associated Deformity of Lower Extremities.*

Case 2 (C. H. 256381). A 2-year-old boy was admitted on October 15, 1941, with the complaint of paralysis of the lower extremities and a lump on the back (Fig. 13). There was no hydrocephalus and the patient was normally alert and responsive. On the 9th hospital day the meningocele was excised and closure was carried out under tension. Seven days later a cerebrospinal-fluid leak developed from the central portion of the incision. Sulfadiazine was started by mouth and an attempt was made to close the leak by resuturing the wound. Three weeks later a third attempt was made and the leak was satisfactorily closed. A lumbar-puncture needle was passed into the upper lumbar subarachnoid space according to the technic described above and 200 to 300 cc. of cerebrospinal fluid was drained every 24 hours for 7 days. At the end of this time the wound was firmly healed. There have been no further complications. It seems reasonable to assume that, without the continuous drainage above the site of the incision, healing would not have occurred and infection would finally have developed.

Summary

The essential features of the satisfactory treatment of congenital cranial and spinal protrusions are the selection of patients suitable for operation, simple removal and repair of the defect adapted to the location, size, and shape of the protrusion and meticulous postoperative care. It should be emphasized that a definitely hopeless prognosis should very rarely be given at the first examination.

References

1. Ingraham, F. D., and Swan, H. Spina bifida and cranium bifidum. I. Survey of five hundred and forty-six cases. *New Eng. J. Med.* 228:559-563, 1943.
2. Dandy, W. E. Operative treatment for certain cases of meningocele (or encephalocele) into orbit. *Arch. Ophth.* 2:123-132, 1929.
3. Penfield, W., and Cone, W. Spina bifida and cranium bifidum: results of plastic repair of meningocele and myelomeningocele by new method. *J. A. M. A.* 98:454-461, 1932.
4. Ingraham, F. D., and Campbell, J. B. Apparatus for closed drainage of ventricular system. *Ann. Surg.* 114:1096-1098, 1941.

ISOIMMUNIZATION WITH Rh FACTOR IN ACQUIRED HEMOLYTIC ANEMIA*

Report of a Case

William Dameshek, M.D.,† and Philip Levine, M.D.‡

Boston, Massachusetts, and Newark, New Jersey

THE following case of acquired hemolytic anemia is reported because of several unusual features, among which was the development of an anti-Rh agglutinin with subsequent violent transfusion reactions. The presence of immune hemolysins in cases of acquired hemolytic anemia has been noted by Dameshek and Schwartz[1-3] in previous communications. These observers produced hemolytic anemias of varying degrees of severity in guinea pigs by the injection of a heterohemolytic serum.[2] Although many cases of acute hemolytic anemia, with and without hemolysins, are cured by splenectomy, others fail to respond. The opinion was expressed by Dameshek and Schwartz[3] that the continued hemolysis in some cases might be due to the development of isoimmunization as the result of repeated transfusions of blood. In the present case, successive transfusions finally resulted in the development of extreme and almost fatal hemolytic reactions. Subsequent analysis of the patient's and donors' blood revealed that the patient (Group O, Rh–) had become immunized by Rh agglutinogen as evidenced by the presence in the patient's serum of anti-Rh agglutinins. Splenectomy revealed intense myeloid metaplasia, and biopsy of the liver showed an extreme erythroblastic reaction, suggesting the histologic picture of erythroblastosis foetalis. Shortly after splenectomy, the patient died of acute (toxic) necrosis of the liver.

*From the Joseph H. Pratt Diagnostic Hospital and the Blood Laboratory, Boston Dispensary, Boston, and the Division of Laboratories, Newark Beth Israel Hospital, Newark, New Jersey. Aided by a grant from the Charlton Fund, Tufts College Medical School.

†Professor of clinical medicine, Tufts College Medical School; visiting physician and consulting hematologist, Joseph H. Pratt Diagnostic Hospital, Boston.

‡Chief of Serological Laboratory and transfusionist, Newark Beth Israel Hospital, Newark, New Jersey.

Case Report

E. P., a 49-year-old housewife, was admitted to the Joseph H. Pratt Diagnostic Hospital on November 20, 1941. The family and past histories were irrelevant. She had given birth to one child without incident 18 years previously. In 1938, because of a sore throat she was given sulfanilamide. A toxic rash shortly developed. Since this illness, the patient had complained of fatigue and weakness, and had seen her physician on numerous occasions. However, she managed to continue her regular duties until July, 1941, when, during a visit to the mountains, she complained of a throbbing headache, and developed vomiting and diarrhea. On returning home, she consulted her physician, who found that she was anemic and prescribed iron and liver extract. No response occurring, she was admitted to the Mercer Hospital (Trenton, New Jersey) on August 28, 1941, where she was found to have a hemoglobin level of 29 per cent and a red-cell count of 1,460,000. Transfusions of compatible blood (Group O) were given on August 28, 29 and 30 without incident. On September 2, the hemoglobin was 52 per cent and the red-cell count 2,770,000. Despite this improvement, three transfusions, each of 300 cc., were given on September 4, 5 and 6 from the same donors, again without reaction. On September 13, the hemoglobin was 51 per cent, and the red-cell count 2,630,000. Four transfusions were again given on September 17, 18, 19 and 20, each of 500 cc. and all from

Group O donors whose bloods were compatible by the slide cross-matching technic. Severe transfusion reactions began with the September 18 transfusion (the eighth). This transfusion and those on the 19th and 20th were followed by violent reactions characterized by high fever, marked jaundice and tenderness in the splenic region.

The patient's condition became rapidly more critical. On September 23, the hemoglobin had dropped to 34 per cent and the red-cell count to 1,700,000. Another transfusion was ventured on September 27, and was fortunately without reaction. However, the patient's condition continued precarious, with increasing anemia, jaundice and fever. On October 1, normoblasts were first noted in the blood smear. On October 4, a consultant thought that "a hemolytic anemia would seem to best fit the picture" and suggested continuance of liver extract and the avoidance of further transfusions. He stated his belief that splenectomy was too great a risk to be undertaken. Following a transfusion of 250 cc. on October 24, the patient became semiconscious, greatly jaundiced and confused; the hemoglobin dropped to 15 per cent and the red-cell count to 800,000. Injections of hypertonic glucose given intravenously were followed by gradual improvement and a rise in the blood levels on November 12 to a hemoglobin of 36 per cent and a red-cell count of 1,800,000.

On November 19, when first seen by one of us (W. D.), the patient was extremely pale and moderately icteric. The heart appeared slightly enlarged, and a systolic murmur was present. The liver edge was readily felt three fingerbreadths below the right costal margin and a rounded, firm splenic edge extended a handbreadth below the left costal margin. The clinical diagnosis of acquired hemolytic anemia was made and the patient was transferred to the Pratt Diagnostic Hospital for further study and treatment.

On admission, the patient showed hemoglobin values of 3.6 to 3.8 gm. (23 to 24 per cent), red-cell counts of 1,390,000 to 1,650,000, platelets 775,000, reticulocytes 22.5 to 49.3 per cent, and a white-cell count of 8150, with 53 per cent mature neutrophils, 14 per cent immature neutrophils, 27 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The hypotonic sodium chloride fragility was 0.48 to 0.20 per cent and the acid fragility (Ham) test negative. The urine showed small amounts of bilirubin and 2.8 mg. of urobilinogen excretion per day (normal 1 to 3 mg.). There was no urinary hemoglobin (benzidine test), but a small amount of hemosiderin was present. The blood bilirubin gave both direct and indirect reactions and varied between 3.1 and 4.0 mg. per 100 cc. The fecal urobilinogen content was 716 mg. daily (average of 4-day sample), and the hemolytic index[4] was thus approximately fifteen times normal. The blood prothrombin was 35 to 40 seconds (normal control, 25 to 30 seconds). X-ray films of the chest showed a slight increase in the lung markings and marked dilatation of the heart, which was thought to be due to the anemia.

The patient's blood was Group O and Rh–. The serum contained no autoagglutinins or isohemolysins, but preliminary tests showed the presence of a strong atypical isoantibody that agglutinated the red cells of 19 of 34 Group O individuals. It was suspected that this isoagglutinin might correspond to the anti-Rh agglutinin, and in most cases tested there was a direct correlation between the reaction of this serum and those of two known human anti-Rh testing serums. However, because of the several discrepancies noted, further immunologic tests were performed in the laboratories of the Newark Beth Israel Hospital. These tests showed two types of agglutinins, a variety of the anti-Rh warm agglutinin, now called anti-Rh_2, and a cold agglutinin. These are discussed below.

It was thought that the patient had become isoimmunized against the Rh agglutinogen as the result of the numerous transfusions that had been given. Through the co-operation of the patient's husband and the Mercer Hospital, blood was obtained from all the donors previously used, and these samples were tested for the Rh factor. The results are shown in Table 1 and indicate the likelihood of isoimmunization by Rh+ blood, the patient herself being Rh–. The patient's family represented an example of the rare double Rh– mating, both the husband and the son being Rh–. The transfusions of donor J. (Rh+), given on August 30 and September 6, were apparently sufficient to induce isoimmunization, since the administration of Rh+ transfusions on September 18, 19 and 20 were followed by violent hemolytic reactions. When another Rh+ transfusion was given on October 4, death almost occurred.

In Boston, Group O compatible Rh– donors were obtained, and transfusions of 500 cc. were given on November 25 and 28, without incident. The patient was then transferred to the care of Dr. Leland S. McKittrick at the Palmer Memorial Hospital, where splenectomy was performed under Avertin and cyclopropane anesthesia on December 1. The postoperative course was at first satis-

TABLE 1. *Summary of Data on Transfusions.*

No. of Transfusion	Date	Name of Donor	Amount of Blood Given	Donor's Blood Group	Patient's Red-Cell Count	Reaction to Transfusion
			cc.		$\times 10^6$	
1	8/28	W. H. P.	500	O, Rh–	1.46	None
2	8/29	R. P.	500	O, Rh–		None
3	8/30	J.	500	O, Rh+		None
4	9/4	W. H. P.	300	O, Rh–	2.77	None
5	9/5	R. P.	300	O, Rh–		None
6	9/6	J.	300	O, Rh+		None
7	9/17	Je.	500	O, Rh–	2.63	None
8	9/18	M.	500	O, Rh+		Moderate
9	9/19	R.	500	O, Rh+		Increasing jaundice
10	9/20	D.	500	O, Rh+		Extreme, with chill and marked jaundice
11	9/27	F.	500	O, Rh–	1.70	None
12	10/4	R.	250	O, Rh+	.80	Severe abdominal pain, hemoglobinuria, jaundice, confusion and so forth
13	11/25		500	O, Rh–	1.50	None
14	11/28		500	O, Rh–	1.75	None
15	11/30		500	O, Rh–	1.70	None
16	12/1		500	O, Rh–		None (splenectomy)
17	12/3		500	O, Rh–	1.86	None
18–19	12/5		1000	O, Rh–	2.08	None

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factory, but the patient then became rapidly more icteric and drowsy. The red-cell count dropped precipitously, — from 1,860,000 on December 3 to 800,000 on December 4, — and the reticulocyte percentage fell from 31.5 per cent on December 2 to 1.9 per cent on December 8. Despite several transfusions from Rh− donors, intravenous fluids and so forth, the patient's condition rapidly became worse. On December 8 the bilirubin value was 28.9 mg. per 100 cc. and the red-cell count was 740,000. The patient died on December 9 in coma.

The spleen, which weighed 750 gm., showed hemosiderosis and myeloid metaplasia with large islands of erythroblastic cells and rather few leukocytic cells; two necrotic areas, probably due to previous infarctions, were also present. Hemolysis of red cells, both within and without the sinusoids, together with agglutinated masses of red cells, was seen. A section of liver removed by biopsy at the time of splenectomy also showed myeloid metaplasia with erythroblastosis predominating. The histologic appearance of the liver was strikingly similar to that seen in erythroblastosis foetalis.

Autopsy. Sections of the liver showed extensive necrosis, the appearance being greatly different from that of the biopsy specimen (the acute necrosis may have been related to the Avertin given as a primary anesthetic agent prior to splenectomy). Evidences of myeloid metaplasia were present in the kidney, adrenal glands, lymph nodes and so forth.*

Comment

This case illustrates the development of isoimmunization following repeated transfusions. The recent investigations of Landsteiner and Wiener[5] and of Levine et al.[6-10] have demonstrated the presence in human red blood cells of an Rh agglutinogen, its inheritance as a Mendelian dominant and its ability to cause isoimmunization. Two different methods of isoimmunization are possible: isoimmunization of an Rh− recipient by repeated transfusions with Rh+ blood[11] and isoimmunization of an Rh− mother by Rh+ red cells from the fetus in utero via the placenta.[7] The data in this case demonstrate the former. As a result of this isoimmunization, an Rh− woman during pregnancy, having built up an anti-Rh agglutinin, might conceivably suffer from an intragroup hemolytic reaction if transfused with blood from an Rh+ donor; or her serum might react in utero with the fetus's red cells, causing erythroblastosis foetalis. That these contentions are correct has been abundantly shown.[9] Although exact data on the development of isoimmunization of an Rh− recipient through the administration of Rh+ blood are usually lacking, it was possible in the present case to gather data that leave little doubt of isoimmunization by the subsequent development of an anti-Rh agglutinin (Table 1).

*We are indebted to Drs. Shields Warren and E. H. MacMahon for their studies of the gross and histologic specimens. Dr. Warren concluded that the predominant picture was one of hemolytic anemia with erythroblastosis, but that the presence of leukopoietic elements, although probably due to myeloid metaplasia, did not exclude a leukemic process.

The presence of two types of atypical agglutinins is demonstrated in Table 2, in which are recorded the parallel results of three series of tests of the patient's serum with eight selected

Table 2. *Tests with Serum of Patient at Various Temperatures and with Known Human Anti-Rh Serums.*

Cells of Group O Subjects	Series I		Series II		Series III	Known Human Anti-Rh Serums	
	A	B*	C	D†			
	37°C.	20°C.	20°C.	37°C.	5°C.	Serum 1‡	Serum 2§
1	+	+	+	+	+	+	+
2	+	trace	0	±	+++	+	+
3	++	+	+	+	+++	+	+
4	0	+	+	0	+++	0	+
5	0	0	0	0	++	0	+
6	0	+	±	0	+++	0	+
7	0	±	+	0	+++	0	0
8	0	0	0	0	+++	0	0

*Tests with additional incubation at 20°C. for one and a half hours.
†Tests with additional incubation at 37°C. for one and a half hours.
‡Gave 73 per cent positive reactions with random human red cells.
§Gave 85 per cent positive reactions with random human red cells.

Group O cell suspensions; at 37°C. (I A), at 20°C. (II C), and at icebox temperature (III). The readings were all made after one and a half hours' incubation at the stated temperatures.

It is clear that the tests at 37°C. reveal the presence of a variety of the anti-Rh agglutinin (anti-Rh_2) that corresponds closely in specificity to that giving 73 per cent positive reactions with consecutively tested random human red cells.

On incubating Series I at 20°C. and Series II at 37°C., almost complete reproduction of the specific temperature effects could be demonstrated (compare Series I A with II D, and Series II C with I B). Although the nature of the specificity of the agglutinin acting at 20°C. could not be determined, it can be stated that it falls in the general group of cold agglutinins as shown by the reactions in Series III.

The specific behavior of the serum at 37°C. indicates that this variety of anti-Rh agglutinin falls into the group of warm atypical agglutinins of Levine, Katzin and Burnham.[6] As a practical application the recommendation is made that in cases in which isoimmunization is suspected the modified compatibility test be performed. This consists of incubation of a mixture of the patient's serum and the donor's cells (Group O or the same group as the patient) at 37°C. for thirty minutes or longer, followed by light centrifugation and resuspension of the sedimented cells. Under these conditions distinct specific reactions are readily obtained with any serum having warm atypical agglutinins. Furthermore, the less important reactions of the cold agglutinins can be differentiated. By the use of this method it was possible to carry out successful transfusions in the present case by neglecting entirely the reac-

tions at lower temperatures. Obviously, equal significance could not be assigned to the two sorts of agglutinins — warm and cold — in this case.

The three varieties of human anti-Rh agglutinins are discussed by Levine.[12] The standard variety (anti-Rh_1) gives 85 per cent reactions and corresponds closely in specificity with the experimental serum of Landsteiner and Wiener.[5] The other two varieties, anti-$Rh_{1,2}$ and anti-Rh_2, give 87 and 70 per cent reactions and contain several agglutinins, one of which corresponds to the antibody described in this case.

The inadvisability of giving transfusion after transfusion in a case of acute hemolytic anemia is well exhibited in this case, in which groups of transfusions were given even when the patient's condition was relatively good and the red-cell counts had risen to 2,500,000 and to 3,000,000. Not only did the patient almost succumb when the last group of transfusions were given, but it is possible that an irreversible autohemolytic process became established at this time. Judging from the management of 25 cases of acute hemolytic anemia and hemolytic crisis, it is our belief that if three or four transfusions of blood have been without effect on the hemolytic process, other transfusions will also probably be ineffective, and the advisability of splenectomy should be immediately considered, lest the hemolytic process become permanent or the patient have such severe reactions that splenectomy might become either unwise or ineffective.

The myeloid metaplasia of the liver and spleen in this case was probably the result of severe continuing hemolysis with extreme regenerative activity on the part of the bone marrow and reversion to the potential hematopoietic functions of the liver and spleen. Others, notably Jackson, Parker and Lemon,[13] have interpreted similar pictures as being due to agnogenic myeloid metaplasia of the spleen with coincidental hemolytic anemia and have pointed to the inadvisability of splenectomy in such a situation. Since the hemolytic process in this case was undoubted and had become aggravated by severe hemolytic transfusion reactions, sufficient reason appeared to be present for the development of myeloid metaplasia. What is more, the contention of Jackson et al. that an agnogenic myeloid metaplasia of the spleen exists is not borne out by our experience, which indicates that for this to develop the bone marrow must become either aplastic, fibrotic, occupied by foreign tissue or unusually hyperplastic, as in a hemolytic process. Thus in erythroblastosis foetalis, which we consider to be acute hemolytic anemia of the newborn,[14] myeloid metaplasia of the spleen and liver is of common occurrence. The histology of the liver and spleen in the present case resembles closely that seen in erythroblastosis foetalis.

Summary

A patient with subacute acquired hemolytic anemia, when given successive transfusions, finally developed severe and almost fatal hemolytic reactions. Subsequent testing revealed that the patient (Group O, Rh–) had developed isoimmunization to the Rh factor with the presence in the blood of both a warm anti-Rh agglutinin and a cold agglutinin. Transfusions with Rh– blood were without reaction. Splenectomy and biopsy of the liver showed intense myeloid metaplasia of both organs. Death resulted from acute toxic necrosis of the liver, and post-mortem examination also revealed widespread myeloid metaplasia in the presence of severe hemolysis.

Repeated transfusions in cases of acute hemolytic anemia may be followed by isoimmunization and the development of irreversible hemolysis. As a result, splenectomy — which might originally have been curative — may prove ineffective.

References

1. Dameshek, W., and Schwartz, S. O. Presence of hemolysins in acute hemolytic anemia. *New Eng. J. Med.* **218**:75-80, 1938.
2. *Idem.* Hemolysins as cause of clinical and experimental hemolytic anemias, with particular reference to nature of spherocytosis and increased fragility. *Am. J. M. Sc.* **196**:769-792, 1938.
3. *Idem.* Acute hemolytic anemia (acquired hemolytic icterus, acute type). *Medicine* **19**:231-327, 1940.
4. Miller, E. B., Singer, K., and Dameshek, W. Daily fecal urobilinogen output and hemolytic index in diagnosis of hemolytic anemia. *Arch. Int. Med.* **70**:722-737, 1942.
5. Landsteiner, K., and Wiener, A. S. Studies on agglutinogen (Rh) in human blood reacting with anti-rhesus sera and with human isoantibodies. *J. Exper. Med.* **74**:309-320, 1941.
6. Levine, P., Katzin, E. M., and Burnham, L. Atypical warm isoagglutinins. *Proc. Soc. Exper. Biol. & Med.* **45**:346-348, 1940.
7. *Idem.* Isoimmunization in pregnancy: its possible bearing on etiology of erythroblastosis foetalis. *J. A. M. A.* **116**:825-827, 1941.
8. Levine, P., and Katzin, E. M. Isoimmunization in pregnancy and varieties of isoagglutinins observed. *Proc. Soc. Exper. Biol. & Med.* **45**:343-346, 1940.
9. Levine, P., Vogel, P., Katzin, E. M., and Burnham, L. Pathogenesis of erythroblastosis fetalis: statistical evidence. *Science* **94**:371, 1941.
10. Levine, P., Burnham, L., Katzin, E. M., and Vogel, P. Role of isoimmunization in pathogenesis of erythroblastosis fetalis. *Am. J. Obst. & Gynec.* **42**:925-937, 1941.
11. Wiener, A. S. Hemolytic reactions following transfusions of blood of homologous group: further observations on role of property Rh, particularly in cases without demonstrable isoantibodies. *Arch. Path.* **32**:227-250, 1941.
12. Levine, P. On human anti-Rh sera and their importance in racial studies. *Science* **96**:452, 1942.
13. Jackson, H., Jr., Parker, F., Jr., and Lemon, H. M. Agnogenic myeloid metaplasia of spleen: syndrome simulating other more definite hematologic disorders. *New Eng. J. Med.* **222**:985-994, 1940.
14. Dameshek, W., Greenwalt, J. J., and Tat, R. J. Erythroblastosis foetalis — acute hemolytic anemia of newborn. *Am. J. Dis. Child.* **65**:571-582, 1943.

MEDICAL PROGRESS

DIABETES MELLITUS

ELLIOTT P. JOSLIN, M.D.*

BOSTON

THE year 1941 witnessed the first break in the upward curve of mortality from diabetes mellitus in the registration area of the continental United States during the last seven years. The mortality rates from 1935 to 1941 are as follows:

1935	22.2 per 100,000
1936	23.7 per 100,000
1937	23.7 per 100,000
1938	23.8 per 100,000
1939	25.5 per 100,000
1940	26.6 per 100,000
1941	25.4 per 100,000

The explanation undoubtedly lies first of all in the prolongation in the lives of diabetic patients, and secondly in the causes of death of these patients becoming more and more those of the population in general and not specifically related to diabetes. A death from diabetic coma is now a rarity. The possibility exists that statistics of diabetic mortality will not represent in the future so good a guide to the incidence of diabetes in the country as heretofore, because diabetes will be increasingly recorded as a secondary cause of death or, I fear, be totally omitted from the death certificate. For the true mortality among diabetic patients and for the incidence of the disease in the country, it is probable that privately gathered statistics will be increasingly valuable. Perhaps after the war the American Diabetes Association with its growing membership of physicians will attack the problem. That the number of living diabetic patients in the country is rapidly advancing there can be no question. At the George F. Baker Clinic of the New England Deaconess Hospital there were 1831 diabetic admissions in 1941, with a mortality of 1.75 per cent, and 1977 diabetic admissions in 1942, with a mortality of 2.33 per cent. There was no death from diabetic coma.

DIABETIC COMA

Many articles on diabetic coma have appeared, but the data from the George F. Baker Clinic are so extensive and have been so favorable in the last few years that one hesitates to make comparisons where for one reason or another results have not been so good. On March 30, 1943, there had been 83 consecutive cases of diabetic coma since August 21, 1940, with the carbon-dioxide content of the blood 20 volumes per cent or less, without a fatality. The number of such cases reported between August 21, 1940, and July 15, 1942, was 62.[1]

A second report[2] of diabetic coma, with recovery after the administration of 1820 units of insulin, ended with the following comment:

> This case teaches again that diabetic coma is a deficiency state, the deficiency being insulin, and that in deep coma of prolonged duration massive doses of insulin are of prime importance. Other supplementary measures such as artificial warmth, saline infusions, gastric lavage and enemas, while very helpful, take definitely a secondary place to adequate doses of insulin.

It would be wrong to ascribe the success of the treatment of diabetic coma in this clinic to the members of its staff alone. Over and over again in recent months and years the physician outside the hospital, who first recognized the case, has inaugurated aggressive treatment in the home, so that although the patient may have arrived in extremis, a beginning had already been made on which hospital treatment could be built. In proof of the above are the following excerpts from a recent case.

> The patient's local physician saw him at 7:00 p.m., diagnosed diabetic coma, recognized the seriousness of his condition, and gave him 70 units of regular insulin. He was admitted to the Deaconess Hospital 1½ hours later.
>
> On admission the patient was completely unconscious and almost moribund, with feeble gasping respirations at 28 a minute, the deep breathing and air hunger that he later recalled having noticed earlier in the day having disappeared. He appeared in a definite state of shock with a blood pressure of 76/40, flushed face, dry tongue and a strong odor of acetone on the breath. The rectal temperature was 92°F., and the pulse 94. The skin was dry and cold. The bladder was distended almost to the umbilicus. The liver was palpable 2 cm. below the costal margin. The lungs were clear and the heart was normal in size. The eyeballs were so soft that the tension could not be measured by an ophthalmologist even 12 hours after entrance. Lipemia retinalis was looked for but not found.
>
> Blood samples for the determination of the sugar level and the carbon-dioxide combining power were taken; the patient was covered with several blankets, and four warm-water bottles were placed near him, one blanket thickness from the body. The urine gave a red Benedict

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*. Volume III. 678 pp. Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

*Medical director, George F. Baker Clinic, New England Deaconess Hospital, Boston.

test and a ++++ test for diacetic acid, and in consequence 50 units of crystalline insulin was immediately injected.

A preliminary blood-sugar report, 20 minutes after entrance, showed that the blood sugar was above 1000 mg. per 100 cc., whereupon 100 units of crystalline insulin was given intravenously and another 100 units subcutaneously. By this time the final report was ready and showed that the blood sugar was 1230 mg. per 100 cc. and that the carbon-dioxide combining power was 7 vol. per cent.

Huge doses of crystalline insulin were indicated, and therefore within the first 4 hours the patient received 1550 units, 600 of which was given intravenously, the latter because of his poor circulation and obviously poor chance for its quick absorption. By the end of 5½ hours of hospital treatment he had received 1750 units of insulin, to which should be added the 70 units given by his local physician 1½ hours before admission, making a grand total of 1820 units in 7 hours. No more insulin was administered for the next 17 hours.

It is most unlikely that this patient would have survived without having received the original 70 units of insulin an hour and a half before his hospital admission. It is quite possible that 10 units given early equals 100 units after an interval of two or three hours — "a stitch in time saves nine."

In this connection, it should be restated that in the George F. Baker Clinic a case is reported as a coma death if the patient is admitted to the hospital in coma, even if he does not die for days or weeks after recovery from coma. Only in this way is one sure to obtain the true mortality from coma. Not uncommonly a patient may temporarily recover, but the treatment given for the coma may have so injured the liver or some other organ or part of the body that, although death did not actually result from coma, it was a direct sequence of it, either immediate or remote.

Diabetic Children Surviving Twenty Years

Insulin was first administered clinically in 1922. Between 1914 and 1922 the average duration of life of the diabetic child did not exceed two years. It was, therefore, appropriate for Eisele[3] to report from the George F. Baker Clinic 73 patients with diabetes with onset under fifteen years of age who had survived twenty years or more. Seventy-one of these were still living. In March, 1922, there were but 103 living children in this clinic, and the 73 who lived twenty years or more represent 72 per cent of this number. Of the 2 who died, one succumbed at twenty-nine years of age to septicemia following an upper respiratory infection, and the other, with a history of onset in 1886 at the age of eight, died in coma twenty-nine years later, in 1915. Fifty-five per cent of the patients were males. The average age at onset of the diabetes for this group was 9.0 years for the males and 8.7 years for the females. The youngest patient developed diabetes at one year and seven months. The oldest living patient is now forty-one, representing the only one living in the fifth decade; there are 39 in the fourth and 31 in the third decade. On the average, the group showed diabetes for 2.8 years before insulin became available. Heredity was positive in 62 per cent, the highest percentage of heredity yet reached by any group save homologous twins, in which the incidence has been recorded as 63 per cent.

The early appearance of arteriosclerosis was the most important complication. Thirty per cent of the series who were examined roentgenologically showed it, and among 55 per cent of those examined there was moderate to advanced ocular sclerosis. Among these two groups, 70 per cent had either hypertension or albuminuria or both at an average age of twenty-nine years.

Impaired physical development in childhood occurred in 16 per cent of the series. However, the average male adult weighed 146 pounds and was five feet, seven inches and the average female weighed 127 pounds with a height of five feet, four inches. Infections played a relatively minor role in the lives of these patients, and operative procedures were done with little more hazard than in patients in a nondiabetic group.

The educational achievement of those who make up this series is probably the most striking feature brought out in the study: 42 per cent have attended college, as compared to 7 per cent of the population of the continental United States who are twenty-one or more years of age.

Diabetic Dwarfism

From the George F. Baker Clinic, Wagner, White and Bogan[4] reported the occurrence, classification and management of diabetic dwarfism. The incidence of retardation among 1407 diabetic patients with onset of the disease under fifteen years of age was 8.3 per cent. The characteristics of 4.6 per cent of the entire series of juvenile diabetic patients and 55 per cent of the retarded group were stunted stature, abnormal proportions, delayed differentiation and hypogenitalism. The remainder of the retarded children were classified as follows: transitory infantilism, 27.1 per cent; constitutional dwarfism, 11.9 per cent; undernutrition, 2.5 per cent; congenital anomalies, 1.7 per cent; neglect, 0.9 per cent; and tertiary syphilis, 0.9 per cent. Thyroid extract, parenteral anterior-pituitary extract and testosterone stimulated growth in typical diabetic dwarfism. The increased severity of diabetes that followed endocrine therapy was evaluated. The social and economic importance of the problem was believed to outweigh the danger resulting from increase in severity of dia-

betes, which, after all, was controlled by an increase in the prescribed amount of insulin.

The acceleration of growth, the early onset of puberty and the sexual maturity at the onset of diabetes in childhood were re-emphasized by these authors. The tendency for a decrease in the rate of growth — the occurrence of leanness in boys and obesity in girls in adolescence — during prolonged duration of the disease was reported. Fischer, Mackler and Marks[5] confirmed these observations.

Vitamin deficiencies in diabetic children are reported in 26.8 per cent of the children observed in the camp of the New York Diabetes Association. Freston and Loughlin[6] found vitamin B deficiency commonest. Deficiency of vitamin A or C was usually accompanied by that of other vitamins. Chemical determinations for carotene were normal. Levels for vitamin A or C or both were low in 88 per cent of the cases tested. Poorly controlled diabetes and hepatomegaly were found in those patients who had signs of vitamin deficiency.

Two-Dose Glucose-Tolerance Test

A careful re-evaluation of the two-dose glucose-tolerance test was made by Wayburn and Gray.[7] Obesity was found to impair the ability of patients to endure the strain of the double load imposed by the two-dose test. There was a close relation between values of the blood sugar and the amount of glycosuria. The one-hour blood-sugar value was found to be the best single determination in the diagnosis of diabetes, and the two-hour value in the classification of its severity. Those authors state that the two-dose glucose-tolerance test is relatively free from the influence of the preceding diet so commonly a disturbing factor in a two-hour, single-dose test.

Etiology

Anticipation in the pattern of inheritance in diabetes has been re-emphasized by Woodyatt and Spetz[8]. Colwell[9] promulgates the optimistic theory that diabetes mellitus begins at birth, that inherent features predetermine the average rate of its progress, that its course is approximately half run before the disease is even recognized, and that some years after recognition it may show progressive and permanent improvement.

Adrenal Gland in Carbohydrate Metabolism

Evidence pointing to the importance of the adrenal gland in carbohydrate metabolism has advanced considerably in the last few years. Since 1901 it has been known that the medulla was implicated, but of late the greater role of the cortex has been recognized. Before presenting a review of recent articles, a brief summary of the action of the two anatomic divisions of the adrenal glands may not be out of place.

Adrenalin, the active principle of the adrenal medulla, obtained by Takamine and Aldrich in 1901, when injected subcutaneously into an animal, as first noted by Blum in 1901, leads transitorily to hyperglycemia and glycosuria. This is accompanied by the conversion of glycogen in the liver into sugar and its discharge into the blood stream, thus opposing insulin, which promotes the formation of glycogen in the liver and muscles. The hyperglycemia produced by adrenalin is greatest when the hepatic store of glycogen is at a maximum, as in well-fed animals, whereas in a hepatectomized animal hyperglycemia fails to appear. Adrenalin likewise reduces the glycogen of the muscles. The muscle glycogen is broken down into lactic acid, which in turn is resynthesized in the liver to glycogen, and this glycogen can again be converted into glucose and subsequently taken from the blood stream and can re-form muscle glycogen, thus completing the cycle. When adrenalin is given after a prolonged fast, or when the hepatic glycogen is low, its effect is to increase the glycogen reserve. The antagonism between adrenalin and insulin has long been known and in 1907–1908 was studied by Zuelzer, who went so far as to designate as a unit that amount of the antidiabetic substance in his extract of the pancreas that would prevent the glycosuria caused by the injection of 1 mg. of adrenalin. In fact, today a 1:1000 solution of adrenalin in 0.5-cc. or 1.0-cc. doses is often employed to counteract the hypoglycemia of an insulin reaction. Hypoglycemia was first noted in Addison's disease by Porges in 1910. Diabetes is never produced by adrenalin, and removal of the medullas from both adrenals does not ameliorate diabetes or prevent its appearance when the pancreas is subsequently removed.

Unlike the medulla, the cortex of the adrenal gland is essential to life, and death in ten to fifteen days follows removal of more than about five sixths of the gland. Pregnant animals (the cortex enlarges during pregnancy) and those in heat survive such removal longer. Various hormonal principles are concerned; among these are hormones controlling the distribution of inorganic ions and the permeability of membranes, and others that affect glucose formation and the deposition of glycogen in the liver. Desoxycorticosterone belongs to the former group and has no effect on carbohydrate metabolism, whereas the latter hormones belong to the corticosterone series, similar chemically to the sex hormones, and

control not only carbohydrate metabolism but also the electrolyte balance.*

In 1934 and 1935, Long and Lukens showed that cats and dogs after combined adrenalectomy and pancreatectomy might be kept alive for considerable periods — from eight to thirty-five days — with only slight glycosuria. Ketonuria did not appear. On the other hand, the administration of cortical hormone led to an increase in glycosuria.

In adrenal insufficiency, carbohydrate metabolism is disturbed in three ways: there is an increased oxidation of glucose in the peripheral tissues (muscles); the liver and kidney fail to synthesize glucose from tissue protein, amino acids and lactic and pyruvic acids; and hypoglycemia is present, as well as a failure of the liver to convert glucose to glycogen. Thus a deficiency of the adrenocortical hormones lowers the supply of energy available for the needs of the body: in consequence, the muscles become incapable of performing work, the liver ceases to carry on its normal carbohydrate function, and the kidney fails in some of its activities. If, on the other hand, extracts of the adrenal cortex containing the essential cortical hormones are administered, the reverse of these actions takes place both in the normal and the adrenalectomized animal.

In 1930, Swingle and Pfiffner extracted a substance from the adrenal cortex that, when injected, counteracted the removal of the adrenals, and animals so treated survived indefinitely. Hartman obtained an extract that he called cortin. Subsequently Grollman and Firor obtained a much more potent extract with the help of acetone. Long demonstrated in 1936 that hypoglycemia could be produced by adrenocortical insufficiency, and this was also observed by Grauman in 1938. Kendall and also Reichstein have isolated several closely related steroids, and to one of these, which was peculiarly active in crystalline form, Reichstein gave the name "corticosterone" and assigned it the following formula: $C_{21}H_{28\text{-}30}O_4$. This substance when made synthetically has one less oxygen atom and is called desoxycorticosterone.

The diabetes of a depancreatized animal if adrenalectomized is rendered mild in a manner analogous to what occurs when a depancreatized animal is hypophysectomized. Conversely, Hartman's extract of the adrenal cortex, cortin, given to a normal animal raises the blood sugar and increases the deposition of glycogen. The alleviation of the diabetes in a depancreatized rat as a result of adrenalectomy is due to the absence of cortin, which is diabetogenic, and, in fact, such animals if kept alive by sodium chloride are not diabetic. The administration of cortical extract, corticosterone, dehydrocorticosterone or Kendall's Compound E to either fasted normal or adrenalectomized mice and rats is followed by large increases in liver glycogen and slight hyperglycemia. Over the course of a few hours adrenocortical extract may thus increase the blood sugar by more than 100 per cent.[10] It is also effective by mouth in raising blood-sugar levels. At first it was thought that the gluconeogenesis from protein was of sufficient magnitude to account for all this newly formed carbohydrate, but later work tends to disprove this explanation and to suggest there must be another source, perhaps secondary to failure of carbohydrate utilization. Studies on rat-liver slices likewise indicate that the rate of synthesis of carbohydrate from pyruvate and *d*-lactate is markedly increased by adrenocortical hormone.[13]

In adrenal insufficiency carbohydrate absorption is reduced, and this reduction combined with a possible increased utilization may account for the flattened dextrose-tolerance curves found in patients with Addison's disease.[14]

Adrenocortical hormone favors glycogenesis in the liver, whereas desoxycorticosterone does not. In Bloomfield's[15] case of Addison's disease, desoxycorticosterone acetate failed to produce an increase of blood sugar or glycosuria, a conclusion similar to that reached by McGavack, Charlton and Klotz.[16] Eschatin, on the other hand, administered in large doses for three days did do so. In contrast, insulin may affect favorably the formation of glycogen in muscle.

As a matter of fact, the occurrence of diabetes in association with Addison's disease is rare. Rhind and Wilson[17] found 14 cases in the literature but had doubts regarding 5 of them. A feature of these cases has been their insulin hypersensitivity.

The oral administration of a hormone, according to Grollman,[18] has advantages over the parenteral route in that it simulates more closely the normally continuous passage of the hormone from the gland. Its expense, however, makes it prohibitive.

The manner in which the cortical principles inhibit the utilization of carbohydrate is not known.

Shipley and Fry[19] in 1942 made a special study of the effect of an adrenocortical ketosis and demonstrated that adrenocortical extract, corticosterone, desoxycorticosterone and 11-dehydro-17-hydroxycorticosterone played no part in ketogenesis. Estrogens, which are similar in structural outline to the cortical hormones, increase liver glycogen and the nitrogen excretion of fasted rats, and this is attributed to stimulation of the

*For recent summaries of problems relating to the adrenal cortex, one should refer to Long's[10, 11] and Ingle's[12] comprehensive articles, of which the latter contains one hundred and forty-six references to the literature.

adrenal cortex by their action on the anterior pituitary gland, since they do not produce these effects in adrenalectomized and hypophysectomized animals. The anti-insulin effect of the anterior pituitary, according to Grattan, Jensen and Ingle,[20] is mediated through the adrenal cortex and does this by promoting the formation of glycogen. However, Long et al.[10] do not believe that the diabetogenic hormone of the pituitary gland is entirely mediated through the adrenal cortex, but rather that a synergism exists between the two hormones.

In connection with studies on rats deprived of the pituitary gland or adrenal medulla, Gellhorn, Feldman and Allen[21] assayed the insulin in the blood. In their investigation they used rats deprived of the pituitary gland, rats deprived of the adrenal medullas and rats deprived of both. Space does not permit the giving of details. Insulin was injected intraperitoneally, and sixty minutes after injection the percentage of sugar in the blood was determined. Tests were made both with insulin and with blood. By this means these authors determined that the insulin content of normal human blood is approximately 0.0002 unit per cubic centimeter; that is, in 5000 cc. of blood, the blood content of the human body, the amount of insulin would be 1 unit. In normal dogs fasted for twenty-four hours the blood contained 0.0001 unit of insulin per cubic centimeter, or half as much. Another conclusion from this study was that the only source of insulin that appears in the blood is the pancreas.

Ingle[22, 23] produced glycosuria in normal rats with a forcibly fed high-carbohydrate diet by the injection of large amounts of 17-hydroxy-11-dehydrocorticosterone. Hyperglycemia, the increased excretion of nonprotein nitrogen, marked loss of weight and atrophy of the testes and thymus gland were also observed. Ingle also tested the diabetogenic effect of stilbestrol in forcibly fed normal and partially depancreatized rats, and noted that very small doses were effective in increasing the severity of the diabetic state of the partially depancreatized animals. Doses of 2 gammas and 10 gammas exerted as positive an effect as did larger doses. Since stilbestrol is estrogenic in amounts as small as 0.5 gamma per day, it is apparent that it is a highly active compound from both the physiologic and pharmacologic standpoint. The four estrogens studied manifest diabetogenic activity in smaller doses than do testosterone and methyltestosterone.

In a comprehensive review of problems relating to the adrenal cortex, Ingle[12] states that adrenocortical insufficiency is characterized by hypoglycemia and the depletion of tissues and carbohydrate stores, especially during fasting; secondly, even in animals depancreatized or treated with phlorhizin the glycosuria is diminished by removal of the adrenals; thirdly, in adrenalectomized animals there is diminution of the formation of carbohydrate from protein, as shown by reduction of urinary nonprotein nitrogen; and, fourthly, in such animals there is an abnormal sensitivity to insulin. All these changes can be reversed by treatments with cortical extract, corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone. The deficiencies in carbohydrate metabolism can be restored to normal by injection of these substances, and, moreover, carbohydrate stores of blood and tissues can be raised above normal both in these and in adrenalectomized animals. Finally, the diabetogenic effect is so marked that partially depancreatized rats that show no spontaneous glycosuria can be made to excrete all the available carbohydrate of the diet during the administration of these cortical principles.

The observation of Ingle that normal rats can be made severely diabetic by the administration of 17-hydroxy-11-dehydrocorticosterone has not yet been independently confirmed. Either normal or adrenalectomized animals become abnormally resistant to the convulsive effect of insulin during treatment with the C-11 oxygenated cortical steroids.

Conn and Conn,[24] in an organic case of hyperinsulinism, found no apparent anti-insulin effect or blood-sugar-raising effect from the daily administration of 30 cc. of adrenocortical extract. They go on to say that the amount of this material used to produce a rise in the blood sugar is relatively so large that it may represent a response that is possible only under distinctly abnormal circumstances, and the clinical use of the material is impractical as an insulin antagonist with the adrenocortical extracts now available.

The oral administration of diethylstilbestrol was tested by Allen and Bern[25] with guinea pigs of both sexes, and definite enlargement of the adrenal cortex was observed.

Janes and Nelson[26] formulated a theory to explain why diethylstilbestrol raises the level of the carbohydrate in the rat. Since it is ineffective in either adrenalectomized or hypophysectomized animals, they infer that one or the other of these glands must be involved. They suggest that diethylstilbestrol stimulates the hypophysis to release some factor, possibly adrenotrophic hormone, which in turn stimulates the adrenal cortex to produce a considerable quantity of some cortical hormone or hormones that are characterized by

having an atom of oxygen attached to the eleventh carbon atom. Such hormones are effective in promoting glyconeogenesis and deposition of glycogen in the livers of fasting animals.

Kenyon et al.[27] failed to note a change in blood glucose in a patient who was given testosterone, nor was the slight glycosuria increased. They saw no indication of the diabetogenic properties in testosterone propionate, that had been described by Ingle,[22] using massive doses in the partially depancreatized rat on a high-carbohydrate diet, or of those described by Dolin, Joseph and Gaunt[28] in the partially depancreatized ferret.

The influence of traumatic shock on the blood sugar of adrenalectomized rats treated with adrenocortical extract was studied by Selye and Dosne.[29] Trauma failed to elicit hyperglycemia when the adrenals were absent. When an active cortical hormone was injected into such animals during trauma, a significant rise in the blood sugar occurred and at the same time an increase in resistance to shock.

A clinical case of the association of tumor of the adrenal cortex with diabetes has been reported by Sprague, Priestley and Dockerty.[30] The diabetes of a forty-nine-year-old woman with no diabetic heredity was discovered in 1938. The disease was difficult to control and required protamine-zinc insulin and crystalline insulin up to 125 units daily, without hypoglycemia. There was no acidosis. The fasting blood-sugar level was 375 to 250 mg. per 100 cc. The diet contained 146 gm. of carbohydrate; the blood pressure was 160 systolic, 94 diastolic. In the right upper quadrant of the abdomen, a large, movable mass was palpable. There was no abnormality of the genitalia or secondary sex characteristics. In March, 1941, the mass, which was then the size of a football, was removed. The fasting blood-sugar levels on the third and fifth postoperative days were 107 and 88 mg. per 100 cc., respectively. There was no glycosuria. Insulin was discontinued. On the twenty-fifth postoperative day, an Exton–Rose glucose-tolerance test was carried out with 50 gm. of glucose given fasting and 50 gm. in thirty minutes. Neither the fasting urine nor the urine in sixty minutes showed glycosuria, and the blood-sugar levels fasting, in thirty minutes and in sixty minutes were 85, 122 and 144 mg., respectively. Eighteen months later the patient was still sugar free. Apparently this patient with an adrenal tumor but without other endocrine manifestations secreted only the cortical steroids controlling carbohydrate metabolism.

In 1936, Long[31] discovered evidence of impaired carbohydrate metabolism in half of 55 reported cases of adrenocortical tumor.

Pregnancy

White and Hunt[32] state that the problem of pregnancy complicating diabetes is controversial in four primary respects. First, as regards fetal survival, they ask, Does it deviate significantly from the normal? Secondly, as to the characteristics of the infants of diabetic mothers, is there an infant recognizable as one so produced? Thirdly, as to the clinical course of the mother, is it normal or abnormal, and does it affect the fetus? Fourthly, what is the need for special care of the infant and the mother?

Between January, 1936, and July, 1942, one hundred and twenty-five consecutive pregnancies occurred in 119 different diabetic patients. In 92 per cent of the patients the diabetes was well established prior to the onset of pregnancy, and in only 9 per cent was the diagnosis made during pregnancy.

Maternal mortality was not the problem. There was 1 death, a mortality of 0.8 per cent. Seventeen of the fetuses died, making the fetal mortality 12 per cent. The causes of death were as follows: macerated stillbirth in 6 cases, atelectasis in 6, subtentorial hemorrhage in 2, hemorrhagic disease of the newborn in 1, defect of the skull in 1, and erythroblastosis in 1. Comparable diabetic fetal mortality has varied from this level to as high as 35 per cent, even in the recent reports of Lawrence and Oakley[33] and of Barns,[34] and if one studies the entire forty-week period of pregnancy, it has been as high as 50 per cent.

Characteristics of the infants of diabetic mothers were as follows: oversize was a predominant trait in this series, 80 per cent of the infants exceeding the expected weight for age. Weight was influenced by three factors: body fat, edema and splanchnomegaly. The edema was sometimes visible, sometimes manifested by weight loss, which was excessive, and sometimes manifested through spontaneous diuresis. The enlargement of the organs was most striking in the liver, spleen and heart, less so in the lungs and kidneys, and variable in the pancreas and thymus and adrenal glands.

The significant pathologic changes were as follows: excessive hematopoiesis of the liver and spleen resembling that found in erythroblastosis occurred in 14 of 17 autopsied infants, atelectasis in 13, persistence of fetal glomeruli in 6, and hyperplasia of the islets in 5. Hertig[35] has reported glycogen infiltration of the enlarged heart and Brenner[36] follicular maturation, corpora hemorrhagica and luteinization in the ovaries of female infants of diabetic mothers.

Congenital defects were found in 17 per cent of the 125 cases. They were usually slight, and most often involved the mesenchymatous tissue.

Clinical behavior was characterized by respiratory difficulty, fever, instability, jaundice and difficulty in feeding. Self-correcting hyperglycemia and hypoglycemia were often observed.

The maternal course was abnormal. Forty-two per cent of the 125 mothers had toxemia, and 25 per cent delivered prematurely. Only 0.8 per cent had diabetic coma, and only 0.8 per cent had severe hypoglycemia.

One of three patterns of behavior was observed in abnormal pregnancies: weight gain, edema, hydramnios, albuminuria and hypertension with intrauterine deaths; hydramnios with intrauterine death; and premature delivery and neonatal death without signs of toxemia.

Fetal wastage and an abnormal clinical course could not be correlated with congenital defects or the disturbed chemistry of diabetes, but both occurred with an imbalance of the hormones of pregnancy.

Forty-one of the patients had a normal balance of the hormones of pregnancy and 84 had an abnormal balance. Of the latter, 27 had no corrective treatment and 57 had substitutional estrin and progestin therapy.

When the hormonal pattern was normal, the fetal survival was 95 per cent (39 of 41 cases), the incidence of toxemia 2 per cent, and premature delivery zero. When the pattern was abnormal, the uncorrected fetal survival was 60 per cent (17 of 27 cases), toxemia 52 per cent, and prematurity 40 per cent. When corrective treatment was employed, the toxemias were modified, fetal survival was 92 per cent (52 of 57 cases), and prematurity was 18 per cent. Diethylstilbestrol in doses from 10 to 50 mg. daily and proluton in doses from 5 to 40 mg. daily were used most commonly. The dosage depended on the response of the level of serum chorionic gonadotropin and urinary pregnanediol.

Forty per cent of these patients were delivered normally, 60 per cent by cesarean section. Premature delivery of abnormal cases is recommended by White, with the date of choice the thirty-seventh week.

Oxygen incubation, heat and dehydration were used routinely for the abnormal infants.

From this study, it appeared that when pregnancy complicated diabetes fetal survival deviated significantly from normal, and there was a factor lethal to the infant.

An infant characteristic of the diabetic mother was observed. The picture could be explained more adequately on the basis of a disturbance of sex hormones than on the basis of diabetes.

The clinical course of the mother was abnormal, being characterized by toxemia and premature delivery associated with stillbirth and neonatal death. These abnormalities were predictable and probably caused by an imbalance of the sex hormones. Corrective substitutional therapy modified the abnormal maternal course and raised fetal survival to more than 90 per cent.

Blood Pyruvate and Lactate

In normal persons the ingestion of glucose is always followed by a rise in blood pyruvate, as shown by Bueding, Fazenkas, Herrlich and Himwich,[37] Bueding, Stein and Wortis[38] and Stotz and Bessey.[39] The rise usually reaches a maximum at the end of one hour and returns to a normal fasting range of 1 mg. per 100 cc. at the end of three hours. The average maximum in 27 normal subjects reported by Bueding, Wortis and Fein[40] was 1.5 mg. Stotz and Bessey have considered that this rise in pyruvic acid following ingestion of glucose is reliable evidence of an increase in glucose combustion. According to Klein,[41] fasting pyruvate levels were normal in 27 of 28 diabetic patients and the lactate was normal in 23 of 25. Following the administration of glucose without insulin a delayed slight rise in pyruvate occurred with no increase in blood lactate. When both insulin and glucose were administered, significant increases in both pyruvate and lactate occurred. So far a comparison of the rise in blood pyruvate and the increase in blood lactic acid with the changes in the respiratory quotient that follow the ingestion of glucose has not been reported. Studies carried out at the George F. Baker Clinic[42] this year in co-operation with the Nutrition Laboratory of the Carnegie Institution of Washington and Dr. Elmer Stotz of the Department of Biological Chemistry, Harvard Medical School, were designed, first, to see whether a close correlation existed between the changes in respiratory quotient and the changes in blood pyruvate.

A second important cause of alteration in the blood lactate-pyruvate relation is found in thiamin deficiency. Thus, Stotz and Bessey[39] have reported data both in human beings and in rats that show that the parallel relation between the levels of blood lactate and of blood pyruvate does not hold when the quantity of lactic acid in the blood is above or below 20 mg. per 100 cc. In thiamin deficiency the rise in blood pyruvate above the fasting level is often excessive. In a diabetic patient studied this winter the fasting blood pyruvate was 0.6 mg., and the value rose

to 2.8 mg. after she received glucose. At the same time the blood lactic acid rose from the basal value of 3.8 to 25.3 mg. This patient had had nausea and vomiting constantly for three weeks owing to uncontrolled diabetic acidosis. The possibility existed in this case that some degree of thiamin deficiency was present.

Another object in this study was to compare the results obtained in diabetic patients with and without the use of insulin. Bueding, Wortis and Fein[40] found that in diabetic patients the ingestion of glucose was followed by little or no increase in blood pyruvate. Yet when insulin was given, a very significant rise in blood pyruvate occurred. Bueding, Fazenkas, Herrlich and Himwich[37] injected glucose into normal animals by the intravenous route at the rate of 2 gm. per kilogram of body weight. In depancreatized dogs no rise in blood pyruvate occurred. However, in such dogs, when insulin was administered simultaneously, a marked rise in pyruvate occurred. It was also noted, however, that without insulin when the blood-sugar level was raised from 750 to 950 mg. per 100 cc., an increase in blood pyruvate might occur even without insulin.

A group of 22 diabetic patients and 1 normal subject were studied at the George F. Baker Clinic. In the majority of patients, observations were made on two different days, on one with insulin administered intramuscularly at the same time glucose was given by mouth and on the other without insulin administration. In general, little or no rise in blood pyruvate and blood lactate occurred following the administration of 50 gm. of glucose by mouth without insulin. Usually little or no rise in the respiratory quotient occurred under these circumstances. On the other hand, when insulin was given at the same time as glucose, a striking rise both in the respiratory quotient and the blood pyruvate and lactate took place. The correlation seems well established.

On the other hand, there were 2 patients, a young diabetic man and a mild diabetic woman who had had a thyroidectomy, in whom a considerable rise in the respiratory quotient was observed with a slight, almost negligible, rise in the blood pyruvate and lactate. It is tempting to consider the possibility that in these patients some glucose was oxidized directly without the intermediary stage of pyruvic acid formation. However, Stotz would consider this too speculative in view of the fact that in more than 90 per cent of the group the correlation between a rise in the respiratory quotient and the change in the blood pyruvate and lactate was so close.

In the group studied is included a patient who was in hypoglycemia during the latter part of the metabolism study. The fasting blood-sugar value was 65 mg. per 100 cc. on the day when he received 20 units of insulin in addition to 50 gm. of glucose, and 59 mg. on the day when he received glucose only. His fasting basal respiratory quotients were 0.94 and 0.89 respectively. When he received glucose only, there was no significant rise either in the respiratory quotient or the blood pyruvate, but when he received 20 units of insulin as well as 50 gm. of glucose, the respiratory quotient rose from 0.94 to 1.04.

One patient was studied following the administration of levulose, and it was found that a rise of 0.07 in the respiratory quotient occurred and simultaneously the blood pyruvate rose 0.5 mg. per 100 cc. Further observations are being made with the hope that some further information about the effects of levulose in diabetes may be obtained.

81 Bay State Road

References

1. Joslin, E. P., Root, H. F., White, P., and Marble, A. Diabetic coma. *J. A. M. A.* **119**:1160-1165, 1942.
2. Bailey, C. C. Treatment of severe diabetic coma with 1820 units of insulin. *J. A. M. A.* **121**:255-257, 1943.
3. Eisele, H. E. Juvenile diabetic patient surviving twenty years. *J. A. M. A.* **120**:188-190, 1942.
4. Wagner, R., White, P., and Bogan, I. K. Diabetic dwarfism. *Am. J. Dis. Child.* **63**:667-727, 1942.
5. Fischer, A. E., Mackler, H. S., and Marks, H. H. Long term growth of diabetic children. *Am. J. Dis. Child.* **64**:413-425, 1942.
6. Freston, J. M., and Loughlin, W. C. Vitamin deficiency in diabetic children. *New York State J. Med.* **42**:1833-1837, 1942.
7. Wayburn, E., and Gray, H. Two-dose glucose tolerance test. *Am. J. M. Sc.* **204**:823-838, 1942.
8. Woodyatt, R. T., and Spetz, M. Anticipation in inheritance of diabetes. *J. A. M. A.* **120**:602-605, 1942.
9. Colwell, A. R. Observed course of diabetes mellitus and inferences concerning its origin and progress. *Arch. Int. Med.* **70**:523-531, 1942.
10. Long, C. N. H., Katzin, B., and Fry, E. G. Adrenal cortex and carbohydrate metabolism. *Endocrinology* **26**:309-351, 1940.
11. Long, C. N. H. Discussion of mechanism of action of adrenal cortical hormones on carbohydrate and protein metabolism. *Endocrinology* **30**:870-883, 1942.
12. Ingle, D. J. Problems relating to adrenal cortex. *Endocrinology* **31**:419-438, 1942.
13. Koepf, G. F., Horn, H. W., Gemmill, C. L., and Thorn, G. W. Effect of adrenal cortical hormone on synthesis of carbohydrate in liver slices. *Am. J. Physiol.* **135**:175-186, 1941.
14. Lewis, R. A., Thorn, G. W., Koepf, G. F., and Dorrance, S. S. Role of adrenal cortex in acute anoxia. *J. Clin. Investigation* **21**:33-46, 1942.
15. Bloomfield, A. L. Coincidence of diabetes mellitus and Addison's disease: effect of cortical extract on glycemia and glycosuria. *Bull. Johns Hopkins Hosp.* **65**:456-465, 1939.
16. McGavack, T. H., Charlton, G. P., and Klotz, S. Effect of desoxycorticosterone acetate on glucose tolerance in normal individuals and in patients with Addison's disease. *J. Clin. Endocrinol.* **1**:824-830, 1941.
17. Rhind, E. G. G., and Wilson, A. Diabetes mellitus in Addison's disease. *Lancet* **2**:37, 1941.
18. Grollman, A. Physiological and chemical studies on adrenal cortical hormones. *Symposia on Quantitative Biology*. Vol. 5. 657 pp. Cold Spring Harbor, New York: Cold Spring Harbor Biological Association, 1937. Pp. 313-322.
19. Shipley, R. A., and Fry, E. G. Effect of adrenal cortical compounds on ketosis. *Am. J. Physiol.* **135**:460-463, 1942.
20. Grattan, J. F., Jensen, H., and Ingle, D. J. Effect of pituitary adrenocorticotropic hormone and of corticosterone acetate on insulin hypoglycemia and liver glycogen in adrenalectomized mice. *Am. J. Physiol.* **134**:8-11, 1941.
21. Gellhorn, E., Feldman, J., and Allen, A. Assay of insulin of hypophysectomized, adreno-demedullated, and hypophysectomized-adrenodemedullated rats. *Endocrinology* **29**:137-140, 1941.
22. Ingle, D. J. Diabetogenic effect of stilbestrol in force-fed normal and partially depancreatized rats. *Endocrinology* **29**:838-848, 1941.
23. *Idem.* Production of glycosuria in normal rat by means of 17-hydroxy-11-dehydrocorticosterone. *Endocrinology* **29**:649-652, 1941.
24. Conn, J. W., and Conn, E. S. Metabolism in organic hyperinsulinism: effects of epinephrine on glycemic level and on combustion of carbohydrate. *Arch. Int. Med.* **68**:1105-1114, 1941.
25. Allen, B. M., and Bern, H. Influence of diethylstilbestrol upon adrenal cortex of guinea pig. *Endocrinology* **31**:586-591, 1942.

26. Janes, R. G., and Nelson, W. O. Relation of diethyl-stilbestrol to carbohydrate metabolism in adrenalectomized and hypophysectomized rats. *Am. J. Physiol.* **137**:557-563, 1942.
27. Kenyon, A. T., Knowlton, K., Lotwin, G., and Sandiford, I. Metabolic response of aged men to testosterone propionate. *J. Clin. Endocrinol.* 2:690-695, 1942.
28. Dolin, G., Joseph, S., and Gaunt, R. Effect of steroid and pituitary hormones on experimental diabetes mellitus of ferrets. *Endocrinology* **28**:840-845, 1941.
29. Selye, H., and Dosne, C. Influence of traumatic shock on blood sugar of adrenalectomized rats treated with adrenal cortical extract. *Proc. Soc. Exper. Biol. & Med.* **48**:532-535, 1941.
30. Sprague, R. G., Priestley, J. T., and Dockerty, M. B. Diabetes mellitus without other endocrine manifestations in case of tumor of adrenal cortex. *J. Clin. Endocrinol.* 3:28-32, 1943.
31. Long, C. N. H. Disturbances of endocrine balance and their relation to diseases of metabolism. *Ann. Int. Med.* 9:1619-1627, 1936.
32. White, P., and Hunt, H. Pregnancy complicating diabetes. *J. Clin. Endocrinol.* (in press).
33. Lawrence, R. D., and Oakley, W. Pregnancy and diabetes. *Quart. J. Med.* 11:45-75, 1942.
34. Barns, H. H. F. Diabetes mellitus and pregnancy. *J. Obst. & Gynaec. Brit. Emp.* **48**:707-725, 1941.
35. Hertig, A. Personal communication.
36. Brenner, M. C. Stimulation of gonads associated with hyperinsulinism in infant. *Arch. Path.* **32**:818-824, 1941.
37. Bueding, E., Fazenkas, J. F., Herrlich, H., and Himwich, H. E. Effect of insulin on pyruvic acid formation in depancreatized dogs. *Science* **95**:282, 1942.
38. Bueding, E., Stein, M. H., and Wortis, H. Blood pyruvate curves following glucose ingestion in normal and thiamine-deficient subjects. *J. Biol. Chem.* **140**:697-703, 1941.
39. Stotz, E., and Bessey, O. A. Blood lactate-pyruvate relation and its use in experimental thiamine deficiency in pigeons. *J. Biol. Chem.* **143**:625-631, 1942.
40. Bueding, E., Wortis, H., and Fein, H. D. Pyruvic acid metabolism in diabetes mellitus. *Am. J. M. Sc.* **204**:838-845, 1942.
41. Klein, D. Effects of administration of glucose and insulin on blood pyruvate and lactate in diabetes mellitus. *J. Biol. Chem.* **145**:35-43, 1942.
42. Carpenter, T., Stotz, E., and Root H. F. Unpublished data.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29201

PRESENTATION OF CASE

A seventy-seven-year-old housewife was referred to the hospital because of attacks of severe upper abdominal pain.

Four and a half months before admission the patient first experienced severe sharp pain, like a constricting band, that began at the right costal margin and radiated across the abdomen to the left upper quadrant. This lasted several minutes and then spontaneously cleared when she was propped up in bed. Similar attacks recurred that varied in degree, but bore no apparent relation to activity, meals or diet. The patient was able to carry out her normal duties effectively except during an attack. Recently she believed that the abdomen had become more protuberant. There was no history of nausea, vomiting, jaundice, diarrhea or tarry, bloody or acholic stools. The genitourinary and cardiac histories were not remarkable. The patient was said to have lost 23 pounds during the two years prior to admission.

The past history was not remarkable. A sister died of cancer of the uterus.

Physical examination revealed a fairly well-developed and well-nourished woman who seemed comfortable. The heart and lungs were normal. The abdomen was distended, and there was a slightly tender, round, grapefruit-sized mass in the left upper quadrant extending from the costal margin to a point 2 cm. below the level of the umbilicus. This did not seem to be attached to the liver and did not move with respirations.

The blood pressure was 190 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a hemoglobin of 11.3 gm. and a white-cell count of 9100, with 82 per cent neutrophils, 14 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The urine was normal. A blood Hinton test was negative. The nonprotein nitrogen was 16 mg., and the protein 6.7 gm. per 100 cc.; the chloride was 97.5 milliequiv. per liter.

A chest roentgenogram showed slight atelectasis of both lower lung fields, which was more marked on the left. The heart appeared to be within the upper limits of normal. The aorta was tortuous and slightly calcified in the arch. An intravenous pyelogram demonstrated normal kidney outlines; no definite stones were seen. There was a large soft-tissue mass in the left midabdomen that filled the flank and extended downward to the level of the left iliac crest (Fig. 1). Intravenous dye appeared promptly and outlined nondilated urinary passages. A barium enema passed to the cecum without delay. The huge mass in the left upper quadrant displaced the colon posteriorly and downward. The appendix lay well up under the right colon. No definite evidence of intrinsic disease within the bowel could be demonstrated. A barium meal outlined a normal esophagus. The stomach was low in position and was displaced to the right and anteriorly by a soft-tissue mass 20 cm. in diameter that occupied almost the entire left side of the abdomen. The stomach was adherent to the mass over the middle half of its length, and one portion was flattened along the surface of the mass. No definite ulceration was demonstrable and the mucosa was apparently uninvolved. The third portion of the duodenum and the adjoining jejunum were displaced medially.

On the day after admission, the patient had a typical attack of pain, which lasted several minutes and disappeared when she was propped up in bed. The abdomen was exquisitely tender in the region of the mass. Normal peristalsis was audible during the attack, and the patient was not nauseated and did not vomit.

An operation was performed on the ninth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MERRILL C. SOSMAN†: On physical examination the mass in the abdomen was described as grapefruit sized. This is a conservative estimate of the size of the mass — either a conservative man described it, or a man from California, who is accustomed to large-sized things of all kinds. It is much larger than a grapefruit — over 20 cm. in diameter in the x-ray film.

Older people who lie in bed for a considerable length of time are prone to get small areas of atelectasis in the lung bases, but sometimes we are unable to see them because of the elevation of the diaphragm, particularly in an adipose patient with a protuberant abdomen. There is a triangular area here in the left base. As a rule these atelectatic zones are parallel to the diaphragm and may have a prominence at the lateral end. It may be a triangle simulating a small pulmonary

*On leave of absence.

†Roentgenologist, Peter Bent Brigham Hospital; clinical professor of roentgenology, Harvard Medical School.

infarct, which also frequently occurs in the base. More important is the fact that the rest of the lungs are clear. There is no evidence of metastases, and no elevation of the left half of the diaphragm, which one would expect if this large mass were the spleen. The entire left kidney is well outlined, the lower pole being easily visible through the upper edge of the mass. There is no distortion of the renal pelvis, such as one would expect if this were an intrinsic tumor of the kidney. Occasionally, tumors of this size are primary in the kidney, such as benign adenomas, but they always distort the renal pelvis. The only other tumor of the kidney of this size would be a benign cyst. This usually has a pedicle attached to the kidney, but does not distort the kidney pelvis or the kidney outline.

The barium enema is negative except for the displacement of the splenic flexure, which is lower than the hepatic flexure. The description of the fluoroscopist says that it was "displaced posteriorly as well as downward." I am thinking of two possibilities: one, a large tumor of the tail of the pancreas, and the other, a huge tumor arising in the wall of the stomach, an extramucosal tumor. Tumors arising in the stomach wall ordinarily displace the colon backward, whereas pancreatic tumors are likelier to displace it laterally and perhaps forward. The displacement of the splenic flexure backward favors a tumor arising from the stomach itself.

I think we can rule out tumor of the kidney. I think we can rule out mesenteric cyst. The mesenteric cysts I have seen are quite circular in

FIGURE 1. *Roentgenogram following a Barium Meal, Which Shows a Large Soft-Tissue Mass in the Left Midabdomen That Displaces the Stomach.*

outline, do not displace the stomach in this manner or shape and are more or less posterior to the stomach. And I think one can say this mass is adherent to the stomach over a considerable area. When I first saw this film I thought that this triangular projection from the posterior wall of the stomach probably ran into the mass of tumor. In other words it looked like a funnel-shaped projection into the hilum of the tumor. If that were true it would make a fairly definite case for one of the large tumors of the stomach wall — a leiomyoma or one of the less-differentiated spindle-cell tumors, usually a sarcoma. But another possibility is present — namely, that there simply was an adhesion to the stomach wall, which was stretched around the surface of the tumor. The mobility is another important point. These tumors of the stomach, particularly the huge sarcomatous type of tumor, usually can be moved around the abdomen without much difficulty. As one would expect, primary tumor in the pancreas is much more fixed and less movable. Could we find out if the mass showed any particular mobility?

Dr. Tracy B. Mallory: Mobility was not mentioned in any of the notes.

Dr. Sosman: It says that the mass "did not move with respirations." It does not say whether it could be moved manually. I assume from that that it was at least not freely movable. This is a fairly important differentiating point. At least it has been in the few of these rare tumors that I have seen. I do not believe I can do any better in the differential diagnosis than to say that the two main possibilities here are a primary tumor of the tail of the pancreas — and tumor that big in the pancreas is apt to be degenerated in the center and more or less cystic — and a tumor of the spindle-cell type, either a fibrosarcoma or a leiomyosarcoma, primary in the wall of the stomach. If the mass were freely movable, I should bet on the stomach; and if practically fixed, on a tumor of the tail of the pancreas.

Dr. Mallory: I do not believe there is anyone here who would have an opinion on that.

Dr. Augustus Rose: What was the mechanism of the pain?

Dr. Sosman: I should imagine that the huge mass pressing on some of the vessels, mesenteric vessels or aorta, would produce it. When the patient sat up and relieved the pressure the pain disappeared.

Dr. Richard Schatzki: If this were pancreas would you expect it to be a tumor or a cyst of the pancreas?

Dr. Sosman: A cyst; but they frequently start as adenomas and degenerate in the center, with a large necrotic area and a little tumor around the wall.

Dr. Schatzki: Would you expect so much adherence to the stomach as you describe?

Dr. Sosman: They may be adherent if they become necrotic and develop an inflammatory process in the capsule. One would have to assume that it was necrotic, inflamed and adherent secondarily. The displacement of the duodenal loop to the right, — here is the duodenojejunal junction, and the descending duodenum comes down here perpendicularly to the center of the spinal column, — fits in more with a tumor well posterior in the region of the tail of the pancreas.

This peculiar coarse mottling of the vertebras is of no clinical importance. I looked at the spine to be sure there were no metastases, and I saw these coarse striations, particularly in the twelfth thoracic vertebra. It might be a benign cavernous hemangioma of the bone, which is of no more importance than a birthmark in the skin, or it might be the early phase of Paget's disease — a coarse trabeculation without much increase in density.

Dr. Schatzki: What do you think of the posterior displacement of the colon?

Dr. Sosman: It worries me if I am going to call the lesion a tumor of the pancreas. That fits in better with a tumor of the stomach wall. I cannot on the available evidence decide between the two possibilities.

Dr. William B. Breed: Does the actual size help differentiate the two possibilities?

Dr. Sosman: I do not believe so. Either one could become unusually large, either by degeneration and necrosis of the central portion or by edema and swelling with cystic changes. If I could be sure it was a solid tumor I should be more in favor of its origin in the stomach wall — a leiomyosarcomatous type of tumor. Is that your experience, Dr. Schatzki?

Dr. Schatzki: Yes.

Dr. Sosman: You believe that we can rule out spleen, kidney and mesenteric cyst quite safely.

Dr. Schatzki: Yes.

Clinical Diagnosis

Omental cyst.

Dr. Sosman's Diagnosis

Extramucosal tumor of wall of stomach — leiomyosarcoma or spindle-cell sarcoma?
Cystic tumor of tail of pancreas?

Anatomical Diagnosis

Neurogenic fibrosarcoma of stomach.

Pathological Discussion

Dr. Mallory: The preoperative diagnosis on the operative sheet was recorded as omental cyst. I suppose they meant mesenteric cyst. At operation a large cystic mass was found. It was adherent over a large area of the stomach and actually arose in the stomach wall. It was quite fluctuant and, when cut into, was found to be a necrotic tumor the central portion of which was liquefied and hemorrhagic. Microscopic examination shows a very undifferentiated, spindle-cell sarcoma. There were a few slightly enlarged lymph nodes on both sides of the stomach, which were resected along with the specimen. All of them were free from metastasis. However, these tumors almost never metastasize to lymph nodes; tumor cells travel via the blood stream to the liver. We thought that it was probably a fibrosarcoma rather than a leiomyosarcoma and that, because of the tendency to whorl formation, it was of neurogenic origin.

Dr. Sosman: You say it definitely arose from the stomach?

Dr. Mallory: Yes; at no spot was there any ulceration of the mucosa. In many of these tumors a deep boring ulcer develops into the core of the tumor, but in this case the mucosa was intact.

Dr. Sosman: Is there a fairly high degree of curability in tumors of this type?

Dr. Mallory: Yes.

Dr. Sosman: Are they slow or late to metastasize?

Dr. Mallory: This one is quite malignant so far as they go. I should want to give a guarded prognosis but believe that the patient is probably cured.

Dr. Sosman: Would you advise local postoperative x-ray treatment?

Dr. Mallory: We have little evidence that it does good in cases of spindle-cell sarcoma. I should not be enthusiastic about it.

CASE 29202

Presentation of Case

A forty-nine-year-old housewife entered the hospital because of severe pain in the lower back and left leg.

Approximately one year before admission, without history of previous injury, the patient suddenly developed severe aching pain in the left sacroiliac area, which was relieved by an adhesive strapping and cleared after one week. Three and a half months prior to admission the pain recurred, being referred to the anterior aspect of the left thigh and occasionally to the posterior aspect and calf. The pain was aggravated by coughing and sneezing and by movements of the lower spine. There had been no weakness, numbness, paresthesia or sphincter difficulty. Bed rest, adhesive strapping and leg traction, continued over a period of three months, gave no relief.

The family and past histories were noncontributory.

Physical examination disclosed a markedly obese woman who was obviously uncomfortable. The heart, lungs and abdomen were normal. There was no weakness of the legs. The ankle jerk was diminished on the left. Sensation was normal. Straight leg-raising was approximately normal on both sides and was not painful. There was no tenderness of the spine, sacroiliac region or legs.

The blood pressure was 140 systolic, 80 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a hemoglobin of 12.0 gm. and a white-cell count of 6900. The urine had a specific gravity of 1.010 and showed a + test for albumin; the sediment contained an occasional red cell, 25 white cells, a rare hyaline cast and 20 epithelial cells per high-power field. A blood Hinton test was negative.

An x-ray film of the spine showed considerable decalcification of all the visible bones. The lumbar spine showed slight scoliosis, with the convexity to the right. The first sacral segment was not fused, and there were marked degenerative changes about its articulations, the second sacral segment and the two iliums. There were also rather marked degenerative changes about the sacroiliac joints.

A spinal tap in the third lumbar interspace yielded xanthochromic fluid, which clotted on standing. There was no response to jugular compression, but a good response to cough. This fluid had a total protein of 2400 mg. per 100 cc. Colorless spinal fluid was recovered from the first lumbar interspace, and at this level there was a normal response to jugular compression and the fluid had a total protein of 294 mg. per 100 cc. A spinal-fluid Wassermann test was negative, and the gold-sol curve was 0001233411.

An operation was performed on the eleventh hospital day.

Differential Diagnosis

Dr. James B. Ayer: Can you say anything about the width of the spinal canal or erosion of the lateral masses?

DR. RICHARD SCHATZKI: Just glancing at these films I cannot see any more than the record states. There is no evidence of erosion. There is some osteoporosis and scoliosis, with slight degenerative changes.

DR. AYER: And a defect that is congenital?

DR. SCHATZKI: Yes.

DR. AYER: No evidence of erosion?

DR. SCHATZKI: No.

DR. AYER: Since there is no mention of cells in the spinal fluid, I assume that none were found.

One year before entry the patient's symptoms might reasonably be considered as having been due to sacroiliac or low-back ligament strain. With the advent of pain referred to the anterior thigh that had a sciatic distribution on the same side and was increased by coughing and sneezing, we are forced to consider a spinal or intraspinal rather than a peripheral cause for symptoms.

The demonstration of complete spinal-fluid block is proof that there was a space-filling mass or other lesions, such as meningeal adhesions, causing obliteration of the subarachnoid space; that this obstruction was focal — that is, between the first and the third lumbar vertebra — is indicated by the fact that dynamic studies showed a rise in spinal-fluid pressure on jugular compression at the upper level and on coughing at the lower. The fluid itself was abnormal at both levels, showing a difference in protein content quite characteristic of a noninflammatory focal lesion.

What type of lesion causes focal subarachnoid block and yet fails to cause symptoms that are characteristic of transverse section of the cauda equina?

Malignant tumors cause unilateral symptoms at first; by the time they produce subarachnoid block, the caudal canal is usually filled with cancer and the symptoms are bilateral. Epidural tumor and abscess likewise cause block only when compression from outside the dura is great, and the symptoms bilateral. In considering extradural lesions we must always think of a ruptured disk, but in my experience, block is caused only when the bulge is large and the symptoms are bilateral. Syphilis and tuberculosis give quite a different clinical picture, and the fluid of each contains appreciable numbers of cells.

Two types of tumor not infrequently cause unilateral symptoms, either pain or weakness, and yet are sufficiently large to obstruct fluid pathways — namely, neurofibromas of the nerve roots and dermoid or other congenital tumors originating in the filum terminale. Either tumor may be associated with an anomaly of the spine, such as that demonstrated in this case. Of these two types the neurofibroma remains more focal, the congenital tumor usually filling and enlarging the canal. The latter usually becomes manifest in youth, whereas the nerve-root tumor may appear at any age.

My diagnosis is neurofibroma, involving a sensory root and lying between the first and the third lumbar vertebra on the left.

DR. HENRY R. VIETS: Although Dr. Ayer is too modest to mention it, it was he[1] who first pointed out that the spinal-fluid protein may be increased above a tumor as well as below it.

There is one other point of interest. Tumors growing from the nerve roots in the cauda equina, such as fibromas, are often somewhat mobile. On jugular compression the spinal fluid is forced down against the tumor and traction is exerted on the nerve root from which the tumor arises, thus causing pain in the area it supplies. This is a valuable test for localizing a tumor and for estimating its probable character, and was first described in 1928.[2] I do not know whether the test was carried out in this particular case. If it were positive, one would have expected that the tumor was a neurofibroma attached to a spinal root. The pain is a variation of that brought about by coughing, sneezing, yawning or straining at stool. The test, however, is not specific for neurofibromas attached to nerve roots, for it has been positive in patients with ruptured intervertebral disks.

DR. CHARLES S. KUBIK: Jugular compression caused severe pain in the back and in the anterior aspect of the thigh.

DR. W. JASON MIXTER: That sign also occurs in patients with ruptured disks.

DR. KUBIK: Dr. Mixter will tell us what he found at operation.

DR. MIXTER: A laminectomy was done, with fairly extensive exposure of the second and third laminas, which were removed, and the dura opened. Quite a large sausage-shaped tumor lay within the roots of the cauda equina. The roots were firmly adherent to the tumor and seemed to run through it. It was necessary to sever two fairly large roots in order to remove the growth. I could not make a definite diagnosis from the gross specimen, but I thought it was a neurofibroma.

CLINICAL DIAGNOSIS

Neurofibroma, region of second or third lumbar vertebra.

Dr. Ayer's Diagnosis

Neurofibroma, involving a sensory root and lying between the first and the third lumbar vertebra on left.

Anatomical Diagnosis

Neurofibroma, region of second or third lumbar vertebra.

Dr. Kubik: On histologic examination the tumor proved to be a neurofibroma.

The patient left the hospital about one month after operation, completely relieved of her pain. Since this type of tumor is benign and since the tumor apparently was completely removed, the prognosis should be good.

Occasionally such tumors are multiple, occurring in other nerve roots or in peripheral nerves throughout the body and producing the clinical picture of neurofibromatosis or von Recklinghausen's disease. This patient, however, showed no evidence of the generalized form of the disease.

References

1. Ayer, J. B. Spinal subarachnoid block: its significance as diagnostic sign. Analysis of fifty-three cases. *Arch. Neurol. & Psychiat.* **10**:420-426, 1923.
2. Viets, H. R. Two new signs suggestive of cauda equina tumor: root pain on jugular compression and shifting of lipiodol shadow on change of posture. *New Eng. J. Med.* **198**:671-674, 1928.

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CURRENT MILITARY AND CIVILIAN NEEDS FOR PHYSICIANS

Published elsewhere in this issue of the *Journal* are statements by the surgeons general of the United States Army, Navy and Public Health Service and by the chairman of the Directing Board of the Procurement and Assignment Service concerning the current military and civilian needs for physicians.

It has recently been emphasized in these columns that more physicians must be dislocated and that the majority of these men must be obtained from urban areas. The official releases referred to above confirm these two statements, but they also imply that the medical profession has been reluctant to make the necessary sacrifices. Such an implication is not altogether fair. Vast numbers of physicians of all ages have already volunteered for military or other governmental service, and as more are needed, they will be forthcoming. The medical profession of this country has never failed to assume its responsibilities, and it will not do so now!

PSYCHOTHERAPY

"It has been a profound shock to me on several occasions that the patient preferred to change his doctor rather than his life-style," writes Dr. Charles Hubble in a very readable article, "Charles Darwin and Psychotherapy," in the February 13 issue of the *Lancet*. Dr. Hubble does not mean that he is still being shocked in 1943 but refers to his adolescent days in psychotherapy. The quotation brings to mind such wisdom as is contained in the adage "Let well enough alone"—a way of saying that although a situation might ideally be better it probably would be worse if tampered with. "Let sleeping dogs lie" is another form of admonition in the same general direction, as is James Thurber's advice to "let your mind alone."

In an analysis of Charles Darwin's chronic, almost lifelong, neurotic illness, Dr. Hubble suggests that had the great naturalist been subjected to strenuous psychotherapy of the twentieth-century variety, *Origin of Species* might never have been written. The zealous psychotherapist would have attacked Darwin's neurotic manifestations, would have jostled them about a bit and, unless wise, would have broken down the protective fence behind which Darwin accomplished his great scientific work—all of which emphasizes the fact that, in spite of the awe-inspiring changes produced by science, the psychotherapist should keep in mind the steadying conception of the limits of human modifiability.

Sometimes it is said that psychotherapy should not rest content with the removal of a symptom: it should go on to discovery and elucidation of the underlying cause. On the contrary it might

be said, if one pays due attention to Dr. Hubble's admonition concerning "sleeping dogs," that psychotherapy should not attempt to remove symptoms in some people, except on a level of light reassurance. What is attempted should depend on what is asked for. Darwin did not want to be cured. He asked, in effect, to be reassured that he was sick and needed treatment, but not cure. If he had been cured he would have had to give precious time and energy to innumerable strength-sapping interruptions.

For a man who accomplished so much, Darwin's daily schedule was unusual. He worked only four hours and during the remainder of the time rested on a sofa or took it easy in one way or another. If he attempted anything outside his established routine he suffered with excitement or a stomach upset. His nights were generally poor, since often he could not stop the activity of his mind. But the resting and bad nights did not amount to so many wasted hours. It was during those hours that Darwin contemplated and nourished the ideas that developed into superior attainment. He did what Harvey Cushing once advised — took time for contemplation so that ideas might be properly fertilized.

Dr. Hubble interprets Darwin's chronic illness as an unconscious means of husbanding energy for his work. One with a direct, honest approach to life might ask why Darwin needed to use subterfuge, unconscious or conscious. Why did he not frankly state that he required so much time for his work and that he had neither the inclination nor the energy for occupations that seemed to him noncontributory? The answer to this, thinks Dr. Hubble, lay in Darwin's great kindliness and sensibility. It would have taken a ruthlessness and unrefined selfishness, of which Darwin was not capable, to say forthright to family, friends and professional associates that he did not have time to give them.

Whether or not the interpretation of Darwin's illness is valid, the sanguine psychotherapist should remember that what is looked on as being neurotic illness is sometimes the best adjustment that can be made by the particular person. Most people with neurotic troubles are not geniuses conserving their strength, but some of them have made certain peculiar adjustments because of biologic necessity and not because of a blind stumbling into disease.

If people could honestly and openly accept, and if their environments would permit them to accept, their limitations, there would be less psychologic impulsion toward neurotic development, but such acceptance requires a hardiness or an ingenuousness not frequently found. Ingenuousness is a childlike quality, and the maturing process in a world of material values does not nurture it. Also, a part, the ambitious part, of the person's very nature may destroy it.

Some people jump, not through hoops, but when startled. The threshold for visceroautonomic reactions may depend on innate, constitutional or hereditary determinants as well as on the influence of environment and circumstance. Instability of psychosomatic reflexes does not necessarily indicate a psychogenic origin for the instability. Dr. Hubble rightly considers this possibility in his analysis of Darwin's "illness."

Because headaches have no clearly defined or discovered physical cause does not warrant the assumption that they are due to psychogenic factors. A sincere but too ardent therapist might add to his patient's suffering by insisting that he rout by self-searching introspection the cause of his disease, when it never could be routed by such a method since it lies in the biologic and physiologic warp and woof of the personality.

The truth may make us free; however, not knowing what is ultimate truth, physicians should be a little cautious in thrusting their own brand of it down patients' psychosomatic throats.

MEDICAL EPONYM

Volkmann's Contracture

This was first described in 1869 by Professor Richard Volkmann (1830–1889), of Halle, in his section of Pitha and Billroth's *Handbuch der allge-*

meinen und speciellen Chirurgie entitled "Die Krankheiten der Bewegungsorgane [Diseases of the Organs of Locomotion]." The following is the translation of a footnote to a discussion of the pathology of inflammatory muscle contractures in general on page 846:

> The severe contractures of the hand that occur after the application of too tight bandages to the forearm in fractures probably depend in part, or sometimes at least, on just such inflammatory muscle contractures, and not on primary nerve paralysis as the result of pressure. As is well known, these distressing cases of so-called "claw hand" have an almost absolutely bad prognosis. . . . The contracture always develops very rapidly, and in a few weeks attains the most marked degrees that may result in ulcerative penetration of the palm by the fingernails. In paralytic contractures, nothing resembling such acute contracture formation is ever seen.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

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CASE HISTORY: BLINDNESS IN A PREMATURE BABY

M. S. was brought to the office at six months of age because of unsatisfactory development, both physically and developmentally. She was delivered by cesarean section three months before term because of continued excessive maternal bleeding. At the operation a low-attached placenta, about half-separated, was found.

At birth the infant weighed 2 pounds, 5 ounces, and was very feeble. She was kept in a Hess bed, at first with the administration of oxygen, for two months, when she weighed 5 pounds. When she was taken home from the hospital, coarse nystagmoid movements of the eyes were noticed.

From the time she went home she did not do well nutritionally, gaining only about 1 ounce a week for two months. At four months she was returned to the hospital where it was found that the hemoglobin level was 35 to 40 per cent and treatment with elixir of ferrous sulfate was begun. In three weeks she gained 10 ounces, and in a month the hemoglobin was 68 to 70 per cent. During the first six months she slept almost continuously.

At six months the infant weighed 9 pounds and seemed to follow light with both eyes, but the eye movements were irregular. A red fundus reflex was seen in each pupil. Tonic neck reflex postures were maintained most of the time, and she paid little attention to objects placed in her hands.

During the next six weeks she gained 26 ounces but did not pay much attention to light. At that time an obvious gray reflex was obtained in the lower half of each pupil, which occupied the quadrant from about 4 to 7 o'clock and extended nearly to the center of the pupil. The upper half of the pupil showed normal red reflexes. The iris cast a shadow on the gray mass in each eye. The nystagmoid movements seen a month earlier were not nearly so prominent.

At twelve months she weighed 15 pounds and had just cut two teeth. She sat in a chair, but on a firm hard surface toppled over. When bright shining objects were held 6 or 8 inches in front of her she fixed her eyes on them and reached for them with both hands.

Comment. Fibroblastic overgrowth of the fetal blood supply of the lens has been recently reported in both eyes of premature infants with visual defects. It has also been seen, usually in one eye only, in a few full-term infants. In premature infants, obstruction to the optical apparatus is usually discovered when they are about six months of age, whereas in full-term infants it is usually discovered soon after birth. In at least one other premature infant the eyes were examined and normal red fundus reflexes twice recorded in each pupil prior to the observation of the retrolenticular membrane.

Such membranes represent a pathologic overgrowth of the hyaloid apparatus of the fetal eye. This consists normally of an embryonic artery and naked capillaries, which supply the lens during its early development. Ordinarily, the artery and its capillaries atrophy and virtually disappear, but in premature babies, especially twins, and rarely in one eye of full-term babies, they persist and become supported by embryonic fibrous tissue in various parts of their course. If the whole artery persists, as the eyeball grows, traction is exerted on the optic nerve, which is pulled forward into the eyeball, producing a pseudopapilledema, usually accompanied by separation of the retina. Fibrous overgrowth among the capillaries on the posterior surface of the lens produces a more or less complete opaque membrane on its posterior surface. The anterior chamber of the eye is often shallow, and the fibrosis may invade the filtration angle, producing a tendency to glaucoma. Under anesthesia, persistent blood vessels may be seen if the membrane is carefully examined and appropriate lenses are used. On account of the tendency to glaucoma, extensive dilatation of the pupil may be dangerous.

The differential diagnosis is important. Cataracts are simulated, but the iris casts a shadow on the retrolenticular membranes, whereas it does not

do so with cataracts. A shallow anterior chamber may lead to error unless care is used. A number of eyes have been enucleated because of a mistaken diagnosis of retinoblastoma. The latter can be excluded by transillumination of the eyeball through the sclera with a small, bright shielded lamp. In the presence of a neoplasm no light shows in the pupil, whereas a membranous obstruction allows the passage of a certain amount of light. The lesions of toxoplasma are usually in the retina itself and move with the posterior surface of the eyeball instead of with the anterior surface.

Treatment has on the whole been unsuccessful. Because of the possible attachment to the optic disk and retina through a persistent hyaloid artery, manipulation of the membrane is accompanied by some danger of separation of the retina. However, successful opening of a trap door in the membrane has been reported. X-ray treatment has not been successful. Diathermy in one case was followed by glaucoma.

There is a tendency for such membranes to involute, and in several infants this has been followed by the development of some sight. In a few, hemorrhage and glaucoma have occurred while a waiting policy was being followed. On the whole this seems the wisest course at present, especially in infants in whom the membrane obstructs only part of the pupil.

DEATHS

DANA — Harold W. Dana, M.D., died of pneumonia at his home in Brookline on May 8. He was in his sixty-sixth year.

Dr. Dana graduated from the Harvard Medical School in 1905, served two years as house officer at the Boston City Hospital, and spent a year and a half in postgraduate medical study, chiefly in Berlin and Vienna. He returned to practice internal medicine in Boston, and served on the Medical Staff of the Boston City Hospital until 1933. He was also associate professor of medicine at Tufts College Medical School.

He was certified as a specialist by the American Board of Internal Medicine. He was also a member of the American College of Physicians and a fellow of the Massachusetts Medical Society and the American Medical Association.

Besides his medical career, Dr. Dana was a man of varied interests, being an amateur watercolor painter of note. He was a prominent member of the New England Historical Genealogical Society and had also served as president of the Massachusetts Society of Sons of the American Revolution and of the Massachusetts Society of the War of 1812.

He is survived by his widow, the former Gertrude Quinn, of Dover, New Hampshire; two daughters, Mrs. Patrick Brady of Brookline, and Mrs. Henry S. Bromley, Jr., of Ardmore, Pa., and five grandchildren.

SCHOTT — Norbert A. Schott, M.D., of Wollaston, died March 25. He was in his forty-first year.

Dr. Schott received his degree from the College of Physicians and Surgeons, Boston. He was a member of the Massachusetts Medical Society and the American Medical Association.

His mother, two sisters and a brother survive him.

WAR ACTIVITIES

PROCUREMENT AND ASSIGNMENT SERVICE

The following statements by the surgeons general of the United States Army, Navy and Public Health Service and by the chairman of the Directing Board of the Procurement and Assignment Service are published by request of the Directing Board to aid its recruiting program.

Statement of the Surgeon General of the United States Army

The Army is increasing in size; more medical officers are required. New units are being formed and many new general hospitals are under construction at many points in the United States. Some basic training must be given to medical officers before they are assigned to purely medicomilitary duty; for this reason, they are needed one or two months prior to actual assignment. For the protection of the health of the civilian population, the quotas for physicians must be fairly distributed throughout the country. Certain states are far behind; they will, it is hoped, do everything possible to furnish their quotas at once.

Statement of the Surgeon General of the United States Navy

In order to plan intelligently I have reviewed the personnel situation in the Medical Department of the Navy. There is a deficit of approximately 900 medical officers for the next six months, based on minimal requirements. The Bureau of Medicine and Surgery calls medical officers to active duty when billets are available and does not build up too large a reserve at any time. Consequently, procurement must go on in an orderly fashion if we are to meet the demands that will be placed upon us as the offensive fighting develops. We cannot afford to have the deficit increase beyond its present level; if it does we shall not be able to give first-class medical service to our wounded.

The Medical Department of the Navy is charged with maintaining the health of all the personnel of the Navy and the Marine Corps; in addition it must care for the dependents of the officers and men. We look to the medical profession of our nation to come forward with the available doctors that can be spared from civil life to aid in our military necessity. In the main, the profession has responded nobly. There are some localities where this is not so. In those localities the medical profession should cause the pressure of public opinion to bear on all eligible doctors and thereby bring to their attention the seriousness of failing to do their patriotic duty.

The medical profession is faced with a challenge of furnishing medical service to the armed forces and to the civil population during the active state of war and in the post-war period, which we hope is not too far distant. Should the profession fail in either regard many

forces may develop that will destroy the practice of medicine as we know it. This would be disastrous and it is something that we cannot afford to allow to come about. In all seriousness, the doctors of medicine in the United States should take stock carefully of their own immediate situations and should give every assistance in planning to see that medicine plays its responsible part in this and coming years.

Statement of the Surgeon General of the United States Public Health Service

During the next twelve months, the United States Public Health Service will require approximately 600 medical officers for full-time active duty in the reserve commissioned corps. These physicians will be recruited on an average of 50 a month — 25 for service in the United States Coast Guard, and 25 for general service.

In addition to the medical officers assigned to the Coast Guard, physicians are needed for duty in the marine hospitals and the medical program of the War Shipping Administration, as well as for detail to general public-health work in state and local health departments, and for such specialized war programs of the Public Health Service as tuberculosis control, venereal-disease control, industrial hygiene and community medical services.

The Public Health Service also expects this year to commission some 5000 physicians in the inactive reserve. These doctors will be available for active duty in the event of acute emergency in their own or nearby communities. They will not be called for active duty unless an acute emergency exists, and will be retained only for the duration of such an emergency. This recruitment of inactive officers is undertaken as a part of the co-operative program of the Public Health Service and the Office of Civilian Defense.

The needs of state and local health departments for physicians have increased greatly during the past year. In January, 1942, it was estimated that state and local health departments would need 600 physicians. As of January, 1943, the exact needs have not been determined, but the Public Health Service has, at the present time, requests from the states for 185 medical officers to be assigned to duty in war areas alone.

According to reports from state chairmen of the Procurement and Assignment Service, as of March 23, 1943, 286 additional doctors for civilian practice are needed in one hundred and seventy-six counties located in thirty-eight states. Another twenty-two counties in the same states reported a shortage of physicians but did not specify the numbers needed. In the remaining ten states, no needs were reported. These one hundred and ninety-eight counties reporting immediate needs represent only 7 per cent of the two thousand, six hundred and fifty-four counties in the thirty-eight states, and only 6 per cent of all counties in the country. Nevertheless, it is apparent that civilian communities are feeling the pinch of the shortage of physicians increasingly, since experience has shown that local needs become acute before they are expressed in formal reports.

In the joint studies made in forty-two areas by the Public Health Service and the Procurement and Assignment Service, it has been determined that 59 physicians and 5 dentists, or 64 medical and dental personnel, are needed in these areas — an average of 1.5 per study. The Public Health Service has been requested to supply 13 of these physicians and dentists, or 23 per cent of the determined need. On the basis of these forty-two studies, it is estimated that 500 physicians and dentists will be needed in three hundred and thirty-two areas to be surveyed in the next coming fourteen months, or by June 1, 1944. It is anticipated that 80 per cent of these, or 400, will be supplied by voluntary relocation through the regular channels of the Procurement and Assignment Service, and that the Public Health Service will be requested to assist in meeting the needs for the remaining 20 per cent, or 100 physicians and dentists. This may be done either through financial assistance to physicians desiring to relocate in areas requiring their services, or through assignment of Public Health Service personnel on request of the proper authorities.

Although it is impossible to project with accuracy the 1943 needs of civilian communities, we must face the fact that the shortage undoubtedly will increase during and after the filling of the 1943 military quotas; and that the chances of meeting civilian needs as well as replacing physicians who die or withdraw from practice because of disability will correspondingly decrease. Furthermore, we cannot predict at this time the possible needs of certain rural areas which now may be adequately supplied but which will require additional public health and medical services during 1943 should the Government move a large number of farm families into these areas for the food-production drive. It is believed that joint action of the Public Health Service and the Procurement and Assignment Service will serve to meet urgent needs in civilian communities.

Statement of the Chairman of the Directing Board of the Procurement and Assignment Service for Physicians, Dentists and Veterinarians

Figures are now complete on the 1942 quotas for supplying physicians of the various states. Forty states have exceeded their quotas. Five states were above 90 per cent of their quotas. Four states — New York, Connecticut, Massachusetts and Nevada — were below 90 per cent of their quotas.

Nevada is the lowest state, but has a total quota of but 35 doctors. It has provided 23 and deserves special consideration because its population is thinly scattered over wide areas.

This statement would not imply any reflection on the patriotism of those members of the medical profession who have been marked available by the Procurement and Assignment Service in the other three states and who have not sought a commission. I would only present the facts and let each one draw from these facts whatever deductions he individually chooses.

Certain unavoidable considerations must be faced in these figures. Four states failed to provide 90 per cent of their 1942 quotas of doctors for the services. Three of these states — New York, Connecticut and Massachusetts — are eastern seaboard states and among the most populous ones in the Union. These populous states have large cities in them which now have more doctors per thousand persons than most other parts of the country. Largely because those doctors marked available by the Procurement and Assignment Service have not sought commissions these states are below their quotas.

Unless more of the doctors found available for military service by the Procurement and Assignment Service in

these cities apply for commissions in the armed forces with reasonable promptness still more doctors must come from rural communities. This will greatly complicate the problem for those communities in their own and other states since many rural communities are already none too well supplied with doctors. Such inequalities in medical service as now exist are in a considerable measure the result of the conditions herein stated and cause occasional problems of rural medical care which become practically insurmountable for the Procurement and Assignment Service with its present limited authority. With all these facts in mind, with the responsibility of medicine to the country and to itself such as it is, the quota figures particularly in New York, Connecticut and Massachusetts should be brought up to par by an intensive effort of the state medical societies through their executive bodies, preferably by an organized state-medical-society campaign.

The provision of doctors for the armed forces is not only the special obligation of medicine but a responsibility which it acknowledges and accepts as its part in the war effort. Each state that has not met its 1942 quota will be kept informed of its position in relation to its quota and its position in relation to other states. Otherwise, a state is denied pardonable pride of satisfaction in meeting its quota or pampered against facing a distasteful position in relation to other states.

MISCELLANY

PNEUMOTHORAX IN THE TREATMENT OF ACUTE MINIMAL TUBERCULOSIS

The intensification of "early diagnosis" campaigns and the widespread use of mass x-raying in war industry and armed service can result only in the discovery of more and more tuberculosis among the apparently healthy. It is obvious that a large proportion of these cases will be preclinical, in the old meaning of the term. Today we must modify our terminology to acknowledge that tuberculosis found early deserves and demands early treatment. Finding the disease in a stage devoid of symptoms imposes on us the obligation so to appraise cases and so to select treatment that development of symptoms will not occur and spread of tuberculosis will be prevented. A recent article emphasizing this point (Kirby, E. G. Pneumothorax in the treatment of acute minimal tuberculosis, *California & West. Med., Tuberculosis Supplement*, July, 1942) is abstracted below.

* * *

In its most characteristic connotation, the term acute minimal tuberculosis implies a recent, or relatively recent, small area of pulmonary infiltration without cavitation. This lesion is most often found beneath the clavicle or in the first or second anterior interspace and is described by the roentgenologist as "soft."

Typically, we might expect the patient to be a healthy-appearing adolescent or young adult who has been in direct contact with a case of active tuberculosis. Cough, sputum, hemoptysis or other classic symptoms have usually not appeared. Constitutional symptoms are absent or are limited to malaise, anorexia or slight weight less. Careful physical examination of the chest is usually negative. The Mantoux test is positive, whereas the sputum or gastric contents may or may not be positive.

Although the foregoing might be described as "typical," each individual case represents a problem for the physician to solve, not only on the basis of his experience in the usual methods of treatment, but also on his knowledge of the social background, economic status and psychologic make-up of his patient. Such important considerations as age, sex, race, occupation, co-existing diseases and length of exposure to tuberculosis must be carefully weighed.

To obtain this information, a period of observation at basal conditions, that is, absolute bed rest, is essential. Whenever possible this period should be spent in a hospital for the tuberculous, away from the distracting influences of the family. This period should be measured in terms of weeks rather than months.

Occasionally, a lesion that roentgenologically seems entirely typical will clear in the space of two or three weeks, indicating a mistaken diagnosis.

The acute early infiltrate is always an unstable lesion — it soon regresses or progresses. Absorption or fibrosis may follow; or there may be rapid or slow progression with caseation, liquefaction and excavation.

The indications for pneumothorax are numerous, but in the opinion of the author, the following are the most important. The production of positive sputum indicates that tissue necrosis has already occurred, and for this reason such cases should be given pneumothorax promptly. Likewise, lesions with x-ray evidence of beginning breakdown should be collapsed immediately.

If the lesion continues to progress on bed rest, immediate collapse is indicated, even though the sputum remains negative. In addition to serial x-ray films, careful pulse, temperature and respiration records, the sedimentation index and a differential white-cell count are valuable indices of the patient's course under therapy.

There are supplementary, more personal indications for pneumothorax, which have not been mentioned so prominently in the literature. The family wage earner may prefer immediate collapse and the attendant shorter period of hospitalization and disability to the more conservative, if equally effective, period of absolute bed rest.

Likewise, the nonco-operative, the unintelligent, or the trouble-making patient may be much better controlled by pneumothorax. In the experience of the author the most difficult patient to handle in the sanatorium is the apparently healthy individual with no symptoms. He finds it boring to maintain himself at bed rest and all too frequently leaves the hospital against medical advice. Many times pneumothorax has been instituted because it seemed the only way to control both the patient and his lesion.

The adolescent girl with minimal tuberculosis requires especially close observation, and if there is any question concerning lack of satisfactory progress, pneumothorax should be done.

Others have listed as advantages of pneumothorax in these cases, the shorter period of hospitalization and disability, the shorter conversion time in case the sputum is positive and the fact that, in their opinion, the end results are better. It should also be emphasized that the physician sees his pneumothorax cases oftener and any change will be detected sooner. He is likewise in a better position to regulate their social and vocational activities.

The chief arguments against pneumothorax are as follows: the inconvenience to the patient, the necessity for the long and expensive period of treatment and, most im-

portant, the danger of complications. Although the latter are rare in minimal cases, pleural effusions, empyema, spontaneous pneumothorax, bronchopleural fistula and nonexpansile lung do occur.

Summary. There is no such thing as a "routine" treatment for minimal tuberculosis. It is equally absurd to say that every case should receive pneumothorax as it is to say that collapse should never be used until the disease becomes moderately or far advanced.

Beginning tissue necrosis, positive sputum and lesions that are progressive on absolute bed rest are, in the opinion of the author, absolute indications for pneumothorax.

Once a small area of pulmonary infiltration has been definitely diagnosed as being tuberculous, the patient should be treated for *tuberculosis*, and not for a "spot on the lung." There are too many patients with "spots on the lung" who only discover that they have tuberculosis when referred to a specialist after their disease has progressed beyond the minimal stage.

If the early-diagnosis campaign is justified, as it most assuredly is, then an early-and-adequate-treatment campaign is likewise indicated.

The adequate treatment of acute minimal tuberculosis does not consist in merely telling the patient to "take it easy." It demands a period of absolute inactivity supplemented by pneumothorax or other collapse procedures as deemed advisable by the attending physician. — Reprinted, in part, from *Tuberculosis Abstracts* (May, 1943).

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1943

Diseases	March 1943	March 1942	Seven-Year Median
Anterior poliomyelitis	3	0	0
Chicken pox	1601	1793	1471
Diphtheria	10	16	14
Dog bite	717	841	754
Dysentery, bacillary	5	0	3
German measles	8210	1182	105
Gonorrhea	327	323	384
Measles	6419	3245	3245
Meningitis, meningococcal	130	24	10
Meningitis, other forms	11	27	*
Mumps	1077	2791	1303
Paratyphoid fever	2	0	3
Pneumonia, lobar	372	516	654
Scarlet fever	2501	1457	1184
Syphilis	479	443	492
Tuberculosis, pulmonary	313	262	285
Tuberculosis, other forms	20	13	28
Typhoid fever	0	2	3
Undulant fever	2	2	4
Whooping cough	875	1004	969

*Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

Geographical Distribution of Certain Diseases

Actinomycosis was reported from: Norfolk 1; total, 1.

Anterior poliomyelitis was reported from: Amherst, 1; Boston, 1; Everett, 1; total, 3.

Diphtheria was reported from: Cambridge, 1; Camp Myles Standish, 2; East Brookfield, 1; Grafton, 2; Lowell, 1; Stoneham, 1; Tewksbury, 1; Wakefield, 1; total, 10.

Dysentery, bacillary, was reported from: Boston, 3; Winthrop, 1; Worcester, 1; total, 5.

Encephalitis, infectious, was reported from: Brockton, 1; Newton, 1; Salem, 1; total, 3.

Lymphocytic choriomeningitis was reported from: Fort Banks, 1; total, 1.

Malaria was reported from: Camp Edwards, 1; total, 1.

Meningitis, meningococcal, was reported from: Attleboro, 1; Barnstable, 2; Bedford, 1; Belmont, 1; Boston, 19; Brockton, 1; Cambridge, 5; Camp Edwards, 32; Canton, 1; Chelsea Naval Hospital, 1; Dartmouth, 1; Easthampton, 1; Easton, 1; Everett, 2; Fall River, 2; Falmouth, 1; Fitchburg, 2; Fort Banks, 4; Fort Devens, 3; Framingham, 1; Greenfield, 2; Hingham, 1; Kingston, 1; Lowell, 4; Malden, 2; Medford, 1; Melrose, 1; Middleboro, 1; Millbury, 1; Needham, 1; Newton, 1; North Reading, 1; Norwood, 1; Plymouth, 2; Quincy, 2; Rockland, 1; Salem, 2; Sharon, 1; Shrewsbury, 1; Somerville, 3; South Hadley, 1; Springfield, 1; Stoughton, 1; Swampscott, 2; Townsend, 1; Watertown, 1; Wellesley, 1; Westover Field, 2; Weymouth, 1; Winchester, 1; Worcester, 6; total, 130.

Meningitis, other forms, was reported from: Boston, 6; Brockton, 1; Cambridge, 1; Lynn, 1; Woburn, 1; Worcester, 1; total, 11.

Paratyphoid fever was reported from: Braintree, 1; Cambridge, 1; total, 2.

Septic sore throat was reported from: Amesbury, 1; Boston, 9; Cambridge, 3; Camp Edwards, 1; Ipswich, 1; Medford, 2; Merrimac, 1; New Bedford, 5; Newton, 1; Wakefield, 2; Westford, 1; total, 27.

Trachoma was reported from: Boston, 2; total, 2.

Undulant fever was reported from: Conway, 1; Greenfield, 1; total, 2.

Meningococcal meningitis continued on the increase during March, reaching the highest figure on the records. Scarlet fever, too, was more prevalent than at any time since 1906, with the exception of March, 1927. Measles and German measles continued at an unusually high level.

The following diseases in addition to the above exceeded their respective seven-year medians: anterior poliomyelitis, chicken pox, bacillary dysentery and tuberculosis (pulmonary).

Under the seven-year median were: diphtheria, dog bite, gonorrhea, mumps, paratyphoid fever, lobar pneumonia, syphilis, tuberculosis (other forms), undulant fever and whooping cough.

Typhoid fever in March repeated the January record of no cases reported. These two months have set up an all-time record.

NOTES

Dr. Charles F. Wilinsky, chief medical officer of the Boston Committee on Public Safety and director of the Beth Israel Hospital, was recently awarded the medal that the Boston City Club presents annually to the resident of Boston, not holding an elective position, who has performed the most meritorious service for the welfare of Bostonians during the year in question. The basis of the award was Dr. Wilinsky's work in organizing the medical section of Boston's civilian-defense effort, as well as his personal services and those of his medical organization during the Cocoanut Grove disaster.

Dr. Douglas A. Thom, director of the Habit Clinic for Child Guidance, Boston, has been granted a leave of absence and is on active duty with the Medical Corps of the Army of the United States, as neuropsychiatric consultant to the Second Service Command, with the rank of lieutenant colonel. Dr. Harvey Spencer, psychiatrist on the staff of the Judge Baker Guidance Center, has been appointed acting director of the clinic.

(Notices on page xiii)

NOTICES

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Haverhill	June 2	William T. Green
Lowell	June 4	Albert H. Brewster
Salem	June 7	Paul W. Hugenberger
Brockton	June 10	George W. Van Gorder
Northampton	June 16	Garry deN. Hough, Jr.
Worcester	June 18	John W. O'Meara
Pittsfield	June 21	Frank A. Slowick
Hyannis	June 22	Paul L. Norton
Fall River	June 28	Eugene A. McCarthy

BOSTON GASTROENTEROLOGICAL SOCIETY

There will be a meeting of the Boston Gastroenterological Society in the Carney Hospital on Wednesday, June 9, at 12 noon. Dr. William E. Browne will present a paper entitled "The Management of Postoperative Distention of Stomach and Bowel, with Demonstration of Cases."

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, May 27

Thursday, May 27

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

Friday, May 28

*9:00–10:00 a.m. The Vascular Lesions in Hypertension Based on Renal Biopsy Studies. Dr. Benjamin Castleman. Joseph H. Pratt Diagnostic Hospital.

Tuesday, June 1

*12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department, Massachusetts General Hospital.

Wednesday, June 2

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

June 4 and 5. American Board of Ophthalmology. Page xii, issue of March 4.

June 9. Boston Gastroenterological Society. Notice elsewhere on this page.

District Societies

MIDDLESEX NORTH

July 28.

WORCESTER NORTH

July 28.

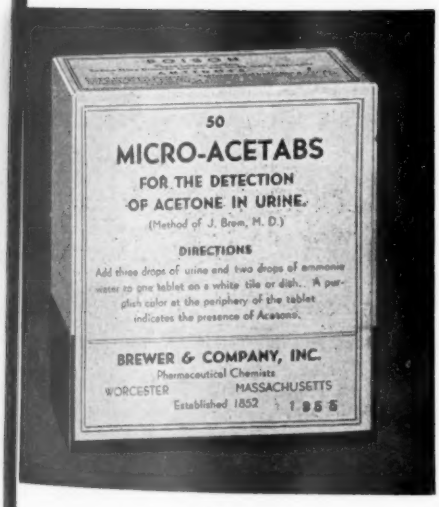
BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Familial Nonreaginic Food-Allergy. By Arthur F. Coca, M.D., medical director, Lederle Laboratories. 8°, cloth, 160 pp., with 20 tables and 12 charts. Springfield, Illinois: Charles C Thomas, 1943. $3.00.

This concise manual describes a new method of diagnosis and treatment of the relatively large group of al-

(Books Received continued on page xv)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lergic diseases in which the usual cutaneous tests fail almost entirely.

Nasal Medication. By Noah D. Fabricant, M.D., M.S., associate in laryngology, rhinology and otology, University of Illinois, College of Medicine. 8°, cloth, 122 pp., with 20 illustrations. Baltimore: The Williams and Wilkins Company, 1942. $2.50.

This small book has been written for the general practitioner and pediatrician, as well as the specialist. It is especially designed for practical use, although it has preliminary chapters on the anatomy and physiology of the nose and its mucous membranes.

Mental Health in College. By Clements C. Fry, M.D., lecturer in psychiatry and mental hygiene and psychiatrist to the Department of University Health, Yale University. With the collaboration of Edna G. Rostow, research assistant, Psychiatry and Mental Hygiene Division, Yale University. 8°, cloth, 365 pp. New York: The Commonwealth Fund, 1942. $2.00.

This monograph, based on long experience, has to do with the emotional and mental behavior of college students.

A Short History of Cardiology. By James B. Herrick, M.D., consulting physician, Presbyterian Hospital, Chicago. 8°, cloth, 258 pp., with 48 plates and a frontispiece. Springfield, Illinois: Charles C Thomas, 1942. $3.50, postpaid.

This short manual on the history of the heart and its diseases covers the seventeenth, eighteenth and nineteenth centuries, from Harvey (1628) to Roentgen (1896). There is prefaced a chapter on the pre-Harveian period, beginning with Hippocrates (460 B.C.).

Lymph Node Metastases: Incidence and surgical treatment in neoplastic disease. By Grantley W. Taylor, M.D., instructor in surgery, Harvard Medical School, associate visiting surgeon, Massachusetts General Hospital, and surgeon, Collis P. Huntington Memorial Hospital and Pondville Hospital; and Ira T. Nathanson, M.S., M.D., instructor in surgery, Harvard Medical School, assistant surgeon, Collis P. Huntington Memorial Hospital, Beth Israel Hospital and Pondville Hospital, and assistant in surgery, Massachusetts General Hospital. With a foreword by Shields Warren, M.D., assistant professor of pathology, Harvard Medical School, Boston. 8°, cloth, 498 pp., with 61 illustrations and 117 tables. London: Oxford University Press, $8.00.

This special monograph provides available information regarding the incidence of lymph-node involvement in various kinds of neoplastic diseases, the factors affecting the incidence, the possibility of cure of metastases by surgical measures and the methods of operating on lymph-node areas. Each chapter has its own bibliography.

Extramural Teaching of Preventive Medicine and Public Health. By Alfred Korach, M.D., lecturer in preventive medicine, University of Cincinnati College of Medicine. *Medical Bulletin of the University of Cincinnati*: Vol. IX (October, 1942). 4°, cloth, 144 pp., with 4 tables. Cincinnati: University of Cincinnati College of Medicine, 1942. $1.50.

This work describes experiments conducted in the College of Medicine of the University of Cincinnati. It gives complete schedules, and also tables indicating the student response to this use of noncredit time.

Regain Your Figure: How to recover the figure after childbirth without "strengthening" exercises. By Lieutenant-Colonel J. K. McConnel, D.S.O., M.C., member of the Chartered Society of Massage and Medical Gymnastics. With a foreword by Cedric Lane-Roberts, M.S., F.R.C.S., F.C.O.G. 12°, cloth, 128 pp., with 28 illustrations. Cleveland: The Sherwood Press, 1939. $2.00.

This work, written for British women, gives a clear exposition of the author's views, based on practical experience and on sound, modern orthopedic teaching. It first appeared in 1938, the year of the launching of the National Fitness Campaign in Great Britain. It is written for the public in nontechnical language and constitutes a complete physical regime for the mother recovering from childbirth.

Biochemistry and Morphogenesis. By Joseph Needham, F.R.S., Sir William Dunn Reader in Biochemistry and Fellow of Gonville and Caius College, Cambridge. 4°, cloth, 787 pp., with 328 illustrations. Cambridge, England: University Press, 1942. $12.50.

This is a comprehensive reference treatise on morphogenesis and related biochemical processes.

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